Title 21—Food and Drugs

CHAPTER I—FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

SUBCHAPTER D—DRUGS FOR HUMAN USE

PART 331—ANTACID PRODUCTS FOR OVER-THE-COUNTER (OTC) HUMAN USE

PART 332—ANTIFLATULENT PRODUCTS FOR OVER-THE-COUNTER (OTC) HUMAN USE

Final Order for Antacid and Antiflatulent Products Generally Recognized as Safe and Effective and Not Misbranded

Pursuant to procedures promulgated in the FEDERAL REGISTER of May 11, 1972 (37 FR 9464), a review of the safety and effectiveness of over-the-counter (OTC) antacid drugs has been undertaken by the Food and Drug Administration.

Notice inviting submission of data and information, published and unpublished, and other information pertinent to the safety and effectiveness of OTC antacid products was published in the FEDERAL REGISTER of January 5, 1972 (37 FR 102). An additional period was allowed for submission of such data and information in paragraph 18 of the preamble to the final procedural regulations published in the FEDERAL REGISTER of January 5, 1972 May 11, 1972 (37 FR 9464).

The conclusions and recommendations of the OTC Antacid Drug Panel and a proposed monograph for OTC antacid drugs was published in the FEDERAL REGISTER of April 5, 1973 (38 FR 8714). A tentative final order pertaining to monographs for OTC antacid and OTC antiflatulent products was published in the FEDERAL REGISTER of November 12, 1973 (38 FR 31260). Notice of a public hearing on the November 12, 1973 tentative final order was published in the FEDERAL REGISTER of January 8, 1974 (39 FR 1359), and the public hearing was held on January 21, 1974. A revision of the November 12, 1973 tentative final order containing a modification of the antacid in vitro test was published in the FEDERAL REGISTER of January 22, 1974 (39 FR 2488).

In addition, a notice of proposed rule making to establish general conditions for OTC drugs listed as generally recognized as safe and effective and as not misbranded was published in the FEDERAL REGISTER of April 5, 1973 (38 FR 8714). The final order on this proposal was published in the FEDERAL REGISTER of November 12, 1973 (38 FR 31258) and became effective on December 12, 1973.

In view of the fact that the regulations for drugs for human use were recodified in the FEDERAL REGISTER of March 29, 1974 (39 FR 11680), the following preamble will identify, as necessary, both prior and current designations for the convenience of the reader.

Objections and requests for a hearing on the tentative final order were submitted by a number of persons. On January 21, 1974, the Commissioner of Food and Drugs held a public hearing to receive oral and written statements on the tentative final order. At the hearing, the Commissioner stated that he would allow 10 days for parties to submit any additional written comments to the Hearing Clerk on any of the hearing issues except that 30 days would be allowed for comments on the proposed effective date of the final order.

The Commissioner stated at the public hearing that the in vitro test in the tentative final order required revision. The test was republished in the FEDERAL REGISTER of January 22, 1974 (39 FR 2488) as a new tentative final order, with further opportunity for objections and/or requests for a public hearing on this aspect of the matter. Nine objections were received on the revised in vitro test. One request for a hearing on the revised test was made, but was subsequently withdrawn.

The Commissioner has reviewed all written and oral comments including the objections filed, the hearing record, and all other comments, pertaining to the tentative final order. Where pertinent, the Commissioner has also again reviewed the scientific information contained in the record of this proceeding. The Commissioner has reached the following conclusions and decisions.

GENERAL COMMENTS

1. There were numerous comments that the antacid monograph should be interpretive, not substantive.

The Commissioner dealt with this issue in paragraphs 85 to 91 of the preamble to the final order establishing the procedures for the OTC drug review published in the FEDERAL REGISTER of May 11, 1972 (37 FR 9464) and paragraph 3 of the preamble to the tentative final order for OTC antacid drugs published in the FEDERAL REGISTER of November 12, 1973 (38 FR 31260). No new points were presented in the comments, and the Commissioner reaffirms the earlier statements. Every court which has to this time considered the issue has found in favor of the substantive application of the OTC drug monographs. The new monographs will be enforceable regulations requiring uniform compliance. The alternative would serve to negate the entire review process. A direct challenge to the legal authority of the Food and Drug Administration to promulgate substantive OTC drug monographs has recently been dismissed in Smart v. Food and Drug Administration (N.D. Calif., C-73-0118-RHS, April 24, 1974), and a second court has also held that section 701(a) of the act authorizes substantive rulemaking, National Nutritional Foods Association v. Weinberger (S.D. N.Y., 73 Civ 3448, April 5, 1974).

2. There were comments that a fuller description of the panel meetings (summary minutes) and/or the transcripts of the panel meetings should be made available.

The Commissioner dealt with this matter in paragraph 37 of the preamble to the final regulation establishing the OTC drug review procedures, published in the FEDERAL REGISTER of May 11, 1972 (37 FR 9464) and paragraph 8 of the preamble to the November tentative final order. The Commissioner has concluded that, when viewed in light of the report and data on file with the Hearing Clerk, the minutes amply serve their intended purpose and the transcript of the closed portion of the Panel meetings should not be made public.

Some of the comments reflected an erroneous impression about the role of a panel in the OTC drug review. Pursuant to section 9(b) of the Federal Advisory Committee Act, the OTC drug review panels are utilized solely for advisory functions. Determinations of action to be taken and policy to be expressed with respect to matters upon which an advisory committee reports or makes recommendations to the Food and Drug Administration must be made solely by the Commissioner. Once the panel has issued its report, its advisory functions are completed. Thus, the purpose of the summary minutes is to maintain a full and accurate record of the panel's reasoning and judgments and to minimize the circulation of speculative and misleading information as to the current status of the review. They constitute part of the public record in order to assist any interested person in formulating meaningful comment on the panel report and the proposed monograph. They have no independent substantive status.

Once the panel has issued its report to the Commissioner, it is the legal responsibility of the Commissioner to review and evaluate it, and to issue a proposed order, tentative final order, and final order reflecting his own conclusions and decisions. This responsibility is independent of the recommendations contained in the panel minutes and report, and it is possible that the Commissioner may adopt conclusions and make decisions contrary to a panel's recommendations.

The transcripts of all open portions of the Antacid Panel meetings are available at cost from the recording company. The Commissioner has concluded that the transcripts of closed portions of the panel meetings should not be released. This conclusion was recently upheld in Smart v. Food and Drug Administration, supra, in which the United States District Court for the Northern District of California held that the deliberative portions of the Antacid Panel were properly closed to the public and that the transcripts of those portions are confidential and are not required to be released under the Freedom of Information Act or the Federal Advisory Committee Act.

The legal justification for closing the deliberative portion of the Antacid Panel's discussions—i.e., the discussion during which the Panel determined its conclusions and recommendations—and retaining the transcripts of those closed portions as confidential may be found in section 10 of the Federal Advisory Committee Act and exemption (5) of the Freedom of Information Act. Section 10(a)(1) of the Federal Advisory Committee Act provides that each advisory

committee meeting shall be open to the public. Section 10(d) then provides that subsection (a)(1) shall not apply to any advisory committee meeting which the head of the agency determines is concerned with matters listed in 5 U.S.C. 552(b), and requires that any such determination shall be in writing and shall contain the reasons therefor.

The authority to close Food and Drug Administration advisory committee meetings has been delegated to the Commissioner, subject to the concurrence of the office of General Counsel 21 CFR 2.120(a)(18). In exercising his authority to close portions of advisory committee meetings pursuant to this delegation, the Commissioner has acted on the basis of the guidelines established by the Office of Management and Budget and the Department of Justice as set out in the FEDERAL REGISTER of January 23, 1973 (38 FR 2306). The Commissioner's formal written determination to close a portion of a meeting is published together with the notice of the meeting in the FEDERAL REGISTER.

The basis on which the purely deliberative portions of the Antacid Panel discussion have been closed pursuant to section 10(d) of the Federal Advisory Committee Act is that the discussion has been concerned with matters covered by 5 U.S.C. 552(b)(5), i.e., internal communications. As the Attorney General's Memorandum of June 1967 on this portion of the Freedom of Information Act states: "* * * internal communications which would not routinely be available to a party in litigation with the Agency, such as internal drafts, memoranda between officials or agencies, opinions and interpretations prepared by agency staff personnel or consultants for the use of the agency, and records of the deliberations of the agency or staff groups, remain exempt so that free exchange of ideas will not be inhibited. As the President stated upon signing the new law, 'officials within the government must be able to communicate with one another fully and frankly without publicity.'"

All of the Antacid Panel members were, of course, consultants to the Food and Drug Administration and, as such, government employees during their period of actual work on the Panel. The discussion within the Panel therefore stands on no different footing than a discussion within an internal FDA staff meeting.

At the same time, the Commissioner recognizes that, consistent with the Federal Advisory Committee Act, advisory committee proceedings should remain open to public view and participation to the maximum extent feasible. It is for this reason that all interested persons were provided an opportunity to make written submissions to the Panel and to present oral views to the Panel. The Commissioner concluded, however, that the deliberations of the Panel during which their conclusions and recommendations are determined could not reasonably be made in open session, and thus that it was essential to avoid undue interference with the regulatory process that they be closed to the public.

The primary reason for closing such deliberative portions of advisory committee meetings is, of course, because of the regulatory nature of the action being considered. With respect to OTC antacid drugs, the issues involved the possibility of specific regulatory action against an individual product—e.g., relabeling the drug, requiring new testing by the manufacturer, or removing the product from the market completely. The Panel discussion included a continuous admixture of deliberations on interim regulatory decisions and thus much of the committee discussion had to be closed to protect the integrity of the regulatory process.

Once the Antacid Panel made its recommendations they were subject to all of the public procedures set out in § 330.10. The Panel's deliberations were the first step in a complex rulemaking proceeding, and there was thereafter still an opportunity for presentation of data and views to the Food and Drug Administration as the proposed regulation was considered pursuant to the public procedures required by the Administrative Procedure Act.

3. There was comment that the administrative record as defined by the Food and Drug Administration in the notice for the public hearing improperly excluded transcripts of the Antacid Panel meetings. The comment stated that the transcripts contained the deliberations of the Panel, including reasonings and facts supporting their decisions, and that it was an essential part of the administrative record. The comment stated that, without such information, it was impossible fully to develop the issues.

The designation of the "administrative record" is in paragraph 82 of the preamble to the final regulations as published in the FEDERAL REGISTER of May 11, 1972 (37 FR 9464). The record includes the panel reports and minutes, but excludes the transcript of the panel deliberations. Elsewhere in this issue of the FEDERAL REGISTER the Commissioner is proposing to amend § 330.10 to incorporate this provision directly in the regulations.

The Commissioner is obligated to base his conclusion with respect to a monograph on the entire administrative record. In the case of the antacid monograph, the Commissioner has not read or referred to or relied upon the words recorded in the transcript of the Antacid Panel meetings. Instead, he has relied solely upon the minutes of the panel meetings, the data and information submitted to and considered by the Panel, the Panel report, the comments submitted on that report, the tentative final order, the objections submitted on the tentative final order, the transcript of and material submitted at the public hearing, and comments filed subsequent to the public hearing. This constitutes the administrative record specified in paragraph 82 of the preamble to the procedural regulations of May 11, 1972, and is the sole basis on which the decisions and orders in the tentative final order and final order were made by him.

Thus, whether the transcript of the OTC antacid panel is made public is irrelevant to the Commissioner's decision on the OTC antacid drug monograph, because it does not form a part of the administrative record on which that decision has been based.

The irrelevance of these transcripts can perhaps best be described by an analogy. The transcripts reflect deliberations and debates among a group of individuals prior to arriving at a final recommendation. The group, in this instance, is deliberating upon recommendations with respect to regulatory policy that will ultimately have the force and effect of law. Their deliberations are therefore directly analogous to the deliberations of a panel of judges of a United States Court of Appeals. It is obvious that the judges who hear a case deliberate among themselves with respect to the issues involved. Moreover, it would not be unusual that there will be several drafts of an opinion, and that the final decision might be quite different from the initial discussions or even tentative drafts. The final opinion written by the court, however, is the only document appealable to or reviewed by the United States Supreme Court. The deliberations of the Court of Appeals, and their various drafts reflecting intermediate considerations and positions, are not a part of the record and are not reviewed by the Supreme Court. The final opinion must stand or fall on its own merits. The same is true of the final report of the OTC Antacid Panel. It stands or falls on its own merits, and is either supported or unsupported by the medical and scientific evidence submitted to and considered by the Panel.

The logic of this position is further compelled by the fact that not all Panel deliberations were recorded or transcribed. Although some transcription or recording occurred with the Antacid Panel, it was necessarily incomplete. Panel members frequently conferred by telephone with each other, discussed matters over lunch and dinner, and talked about them during breaks and in the corridors. Moreover, the major reflective consideration of the issues involved would be likely to have occurred before and after meetings, when the Panel members individually reviewed the data and information and formed their conclusions with respect to it. Thus, any transcript of Panel deliberations would reflect only a part, and perhaps a small part, of the consideration given to the matter, of the reasoning which lies behind the recommendations ultimately made, and thus of the entire deliberative process. It would therefore be highly improper to consider the transcripts of Panel meetings in determining the validity of the final OTC antacid drug monograph.

4. There was comment that the administrative record should not properly be closed prior to the final order, and that a letter of objection providing new information for the public hearing should be part of the administrative record. The comment argued that no notice was given that the ability to introduce new evidence

and information on antacids ended when the comment period on the proposal closed. The comment stated that, if the agency wished to close the administrative record, it should make a change in the monograph procedures.

The Commissioner believes that the existing regulations make it clear that new evidence could only be submitted up through the 60 day comment period on the proposed monograph. The purpose of the hearing before the Commissioner on the tentative final order is solely to review the administrative record already compiled, and not to submit new evidence. However, in view of the fact that the present regulations do not explicitly state this requirement, the Commissioner concluded to accept all proffered information in this instance and to amend the regulations to clarify this matter. An appropriate proposed change in the regulations is published elsewhere in this issue of the FEDERAL REGISTER.

5. There was comment that the phrase "ethical drug" or "ethical labeling" is an inappropriate designation in § 331.31 and § 332.31 (formerly § 130.305(f) and § 130.306(d)) because it is an outmoded term. It was suggested that a more appropriate phrase would be "practitioner labeling" or "labeling for professional person." A comment also objected that, under the monograph, such labeling would be provided only to physicians.

The Commissioner believes that both of these points are sound. Such labeling will be designated in the future as "professional labeling" or "labeling for health professionals". This will include all health professionals who prescribe, administer, or dispense medications.

6. There was comment that the 30 days allowed for comment on the January tentative final monograph was "patently unconscionable and unreasonable", because the comments had to be received by the Food and Drug Administration on the 30th day. It was stated that "private parties cannot be held responsible for the vagaries of the U.S. Mail".

The 30 day period is provided for in § 330.10(a)(7) of the regulations (formerly § 130.301(a)(7)). Requiring the comments to be received at the Food and Drug Administration by the 30th day was done so that the agency could promptly begin preparing for a hearing or final order. Under the circumstances, the Commissioner concludes that requiring the comments to be received within 30 days at the Food and Drug Administration was not unreasonable.

7. There was a comment filed after the hearing requesting that magnesium trisilicate be listed as an antiflatulent in the antiflatulent monograph.

The Commissioner stated in paragraph 67 of the preamble to the tentative final order that any other claimed antiflatulent ingredient should be submitted when the call for data for miscellaneous internal products was published. That notice was published in the FEDERAL REGISTER of November 16, 1973 (38 FR 31696). The Commissioner realizes that magnesium trisilicate was reviewed by the Antacid Panel, but only as an antacid ingredient. Reviewing the submitted magnesium trisilicate antiflatulent data would require reopening the administrative record. Since the Miscellaneous Internal Panel will review all antiflatulents, there is no reason to disrupt the orderly consideration of this monograph. The Commissioner therefore concludes that this matter is properly handled by the Miscellaneous Internal Panel. The person submitting this comment should promptly submit all pertinent data and information to that Panel if he has not already done so.

8. In the comments to the tentative final order, a proposal was made that the Food and Drug Administration establish a "third class of drugs" which would be available only from a pharmacist or pharmacy and for which a pharmacist or pharmacy would maintain a patient dispensing record.

The Antacid Panel never considered the issue of the third class of drugs, and this issue is not properly a part of the OTC drug review. Elsewhere in this issue of the FEDERAL REGISTER the Commissioner is publishing a notice which states his conclusion that there is no health or safety justification for establishing a third class of drugs at this time.

GENERAL CONDITIONS

There were numerous comments on the general conditions for OTC drugs established in § 330.1 (formerly § 130.302). That final order was published in the FEDERAL REGISTER of November 12, 1973 (38 FR 31258) and became effective on December 12, 1973.

9. Most of these comments concerned the question whether § 330.1(i) should be revised to include a reference to pharmacists on OTC drug labels where there is a drug interaction potential.

The Commissioner is publishing his conclusions on this matter elsewhere in this issue of the FEDERAL REGISTER.

10. There was a proposal to add the words "consult your poison control center" to the accidental overdose warning under § 330.1(g) (formerly § 130.302(g)).

The Commissioner is publishing a proposal on this matter elsewhere in this issue of the FEDERAL REGISTER.

11. There was comment that the drug interaction warning contained in § 330.1(i) (formerly § 130.302(i)) had been moved from the antacid monograph to the general conditions for OTC drugs without notice and opportunity for public comment.

The Commissioner published this warning as a proposal in the FEDERAL REGISTER of April 5, 1973 (37 FR 8714), with time for public comment. It was transferred from one section to another because of its broad applicability to all OTC drugs. This procedure was therefore entirely proper. In any event, the Commissioner heard comments on this matter at the January 21, 1974 public hearing and is now publishing a further notice on the matter elsewhere in this issue of the FEDERAL REGISTER.

12. There was comment that the agency has the authority to require the quantitative labeling of active ingredients.

The Commissioner stated in paragraph 11 of the preamble to the tentative final order that such authority does not presently exist under the Federal Food, Drug, and Cosmetic Act. No specific response to this preamble statement was included in the comment received. The regulation requests that manufacturers voluntarily place such information on their label, § 330.1(j) (formerly § 130.302(j)). There are also bills (S. 3012 and H.R. 12847) pending before Congress to amend the act to provide for quantitative labeling of active ingredients for OTC drug products.

IN VITRO ACID NEUTRALIZING TEST

13. A number of written comments were filed on the November tentative final order dealing with the in vitro test procedure proposed in that notice.

The Commissioner notes that the modification of the in vitro test published in the FEDERAL REGISTER of January 22, 1974 (39 FR 2488) answered many of the issues raised. Accordingly, only the comments filed in response to the January republication and revision of the test have been considered in preparing this final order. The only request for a hearing on the revised test has subsequently been withdrawn.

14. One comment urged the Commissioner to add more specifications, such as particular types of equipment and additional controls, to the in vitro test because it has too many variables and cannot be considered a simple test.

The Antacid Panel proposed a simple test for the present and recommended that the Food and Drug Administration and industry do research to find an in vivo test. The Commissioner concurs now and that research should promptly begin on an in vivo test. With that approach in mind, the Commissioner does not believe that the in vitro test should be unnecessarily complicated by requiring special equipment and specifications for which no justifications have been shown.

15. One comment submitted a proposed in vitro test which the comment contended would be reproducible and more like an in vivo test.

The proposed test is also an in vitro test. No data were submitted to show that this test is more accurate or reproducible, or more closely parallels in vivo results, than the in vitro test in the final order. For that reason, the Commissioner believes that it would be inappropriate at this time to consider adopting this proposed in vitro test which no one has had an opportunity to review or comment upon. However, the agency will conduct studies and review the proposed test as it considers the development of an in vivo test.

16. Two comments indicated that the change in the test from the November tentative final order to the January revision resulted in a significant change in philosophy. They noted that the earlier proposal included a titration based on time, and the latter included a back titration technique that removed consideration of time and relative reactivity of the product.

The Commissioner concludes that the new procedure does not eliminate time as a factor. The preamble to the January revision stated that the procedure in the November tentative final order would have been extremely difficult to validate because of the variable time factor in the revised procedure retains the variation in time as a critical test factor in that the product must demonstrate adequate neutralizing capacity within the 15 minutes allowed. The Commissoner concludes that the 15 minute back titration technique is consistent with the clinical significance of the product and its rate of reactivity. As stated in paragraph 34 of the preamble to the November tentative final order, the acid neutralizing capacity of a product is only one factor in selecting an antacid.

17. There was comment that the in vitro test had been burdened with arbitrary modifications that set it potentially at variance with correspondng tests already in the United States Pharmacopeia.

United States Pharmacopeia standards determine strength, quality, and purity of designated products and are not a test of effectiveness. The Food and Drug Administration's in vitro acid neutralizing test is a single test that is dose related, requires the acid neutralizing capacity to be determined in 15 minutes, applies to all products which are labeled as antacids, and is concerned with the product's total effectiveness in terms of its acid neutralizing capacity. The Commissioner therefore concludes that the in vitro effectiveness test is not at variance with the United States Pharmacopeia standards for strength, quality, and purity of certain antacids.

18. There was comment that the preamble to the November tentative final order stated in paragraph 37 that the two United States Pharmacopeia tests were not used because they were only concerned with total consumption of acid and not with duration, whereas the preamble to the January revision stated that the in vitro test must be based on a back titration technique since it was impossible to validate the procedure using the test in the November tentative final order. The comment states that, based on these changes, the Food and Drug Administration test no longer purports to measure a duration of activity and offers no advantages over the United States Pharmacopeia method.

The Commissioner notes that there is no single United States Pharmacopeia method. In fact, for the 12 official products listed as antacids in United States Pharmacopeia XVIII, page xxxix, there are no acid consuming capacity tests identified for five and for the other seven, four use a similar test that differs primarily in the acid used, one uses a very simple test, and the other two have a more complicated procedure that takes four hours for the antacid to neutralize the acid. Basically, the United States Pharmacopeia procedures are for individual products, are not dose related, allow one or more hours for the acid to react with the antacid, and are determinations of strength, quality and purity. As explained above in paragraph 17 of this preamble, the Food and Drug Administration's in vitro test determines effectiveness for all antacid drug products.

19. There was comment that it was inappropriate to include an in vitro acid neutralization capacity test as a basis of general recognition of safety and effectiveness, because there is no substantial evidence to prove that a product which passes the test is safe and effective, nor are there any data correlating the in vitro test to in vivo results. The comment contended that, since there are no data, there can be no basis on which experts can conclude that the in vitro test measures safety and effectiveness.

The Antacid Panel found that there was a substantial scientific basis on which to create an in vitro test for measuring effectiveness. To support their position, they cited seven publications concerning gastric secretion and antacid activity. The Commissioner has reviewed the literature and concurs with the judgment that there are sufficient data on which to base an in vitro test. However, the Commissioner recognizes, as the Panel did, that the industry, academia and agency should promptly seek to develop an in vivo antacid test.

20. There was comment that the in vitro test should not be applied to products that are not designed to neutralize the total stomach acidity. The comment contended that a floating antacid that claims to neutralize the stomach contents that are refluxed into the upper esophageal tract should be tested differently. The comment proposed an in vitro test similar to that published in the November tentative final order.

The Commissioner has found that adequate evidence to prove effectiveness for a product that floats and only reduces the acidity in the upper stomach and lower esophageal tract has not been presented (see paragraphs 60 and 61 below and paragraph 25 in the preamble to the November tentative final monograph). To allow marketing of the product while data are being obtained on this category III active ingredient, the method for measuring the acid neutralizing capacity submitted will be reviewed by the Commissioner as an exemption request to the in vitro test. If adequate data for effectiveness are presented it will be possible to review the proposed in vitro test as an amendment to the monograph.

21. One comment complained that antacid capsules have not been provided for in the test procedures.

The Commissioner concludes that capsules may be tested in the same manner as tablets. This additional provision has been added to the final order.

22. There was comment that the requirement that each antacidl ingredient contribute at least 25 percent of the total effectiveness of the product should not be calculated on the basis of four times the amount of the ingredient present but on the basis of the amount actually contained in the dosage being tested. The percentage of contribution should then be calculated from the amount of acid neutralization of the ingredient in relationship to the amount of acid neutralization of the whole dosage unit.

The Commissioner concurs that this is a more scientific approach. The final order has been changed accordingly.

23. There was comment that the acid neutralizing test is being interpreted in two different ways. One interpretation is that the 25 percent requirement applies to the 5 milliequivalent minimum, i.e., one-fourth of the 5 milliequivalents means that each active ingredient must reduce 1.25 milliequivalents to be considered an active ingredient. Another interpretation is that four times the amount of the ingredient must neutralize the same amount of acid as a total drug product to reach the 25 percent minmum.

The Commissioner advises that the proposed procedure was to take four times the amount of each active ingredient and test it against the total drug product to determine the 25 percent. As now revised, the 25 percent requirement is to be based on a comparison of the acid neutralizing capacity of the amount of the ingredient in the product with the total acid neutralizing capacity of the product (not with the minimum value required by the monograph for an antacid). Thus, the standard for measuring the 25 percent requirement remains the total acid neutralizing capacity of the entire product. As stated in paragraph 22 of this preamble, the Commissioner has amended the test to clarify the basis for calculating the 25 percent minimum.

24. One comment proposed that the number of active ingredients be limited to four and that the 25 percent requirement be deleted. In the 10 days allowed after the hearing, a comment was received which opposed any arbitrary limit on the degree of activity or number of active ingredients allowed in a proprietary medication.

For the reasons stated in paragraph 30 of the preamble to the tentative final order, the Commissioner concludes that each active ingredient should make a minimum contribution of 25 percent of the acid neutralizing capacity to the final product. The 25 percent figure was based on the conclusion that any ingredient in an antacid should contribute to the acid neutralizing effect. If only the number of ingredients were limited, three of the labeled active ingredients could be used in such small amounts that the contribution of each to the product's effectiveness would be insignificant. The consumer would then be misled because the label would list four ingredients when in fact only one made a significant contribution to the therapeutic effect.

The comments have failed to supply any data to support any safety or effectiveness reason for not adopting the proposed 25 percent requirement or for adopting a different requirement. The Commissioner concludes that the 25 percent requirement will provide the consumer with safe and effective antacid

combination drugs that are not misleading.

25. There was comment that the words "magnetic stirrer" were not specific enough because the stirring speed is a critical factor and the shaded pole motor stirrer normally found in laboratories will vary too much. The comment proposed that a direct current motor controlled by a solid state direct current power pack attached to an accurate tachometer be specified.

The Commissioner realizes that stirring speed is important to the evaluation, but is also of the opinion that the laboratory should be given the responsibility of determining how it wishes to obtain the necessary stirring speed. It would be arbitrary for the Commissioner to designate a particular type of equipment if a laboratory can properly conduct the test using other equipment.

26. There was comment that the 100 ml. and 250 ml. beakers are not large enough to accommodate more effective antacids or those which foam.

The Commissioner realizes that many factors effect analytical tests such as the proposed in vitro test. In an effort to standardize the test it has been necessary to designate the beaker size just as do the United States Pharmacopeia and the National Formulary in their methods of analysis. However, the Commissioner recognizes that there may be a manufacturer who cannot test his antacid in these sizes of beakers. A manufacturer may request an exemption stating the size of the beaker he desires to use and data validating the test using the different beaker size.

27. One comment stated that the tablet comminuting device must be specified because the type of device and the speed of action control the amount of surface area and therefore the rate of reactivity of the product.

The Commissioner does not believe that a specific comminuting device should be designated at this time because no data have been presented to show that erroneous results will occur or that the test provides information more closely related to in vivo results if such a device is used. It would be arbitrary for the Commissioner to require the purchase and use of a specific piece of equipment when insufficient data have been collected to determine its effect on the test.

28. There was a comment that "distilled water" should be specified.

The Commissioner agrees, and "distilled water" has been specified in the final order.

29. There was comment that the sieve size should be designated as the United States standard since there are nonstandard sieves available.

The Commissioner agrees, and the United States standard designation has been added in the final order.

30. There was comment that the use of 0.5 and 1.0 Normal hydrochloric acid affects results obtained because the reaction rate of any reaction can be increased by increasing the concentration of the reactants. The comment also pointed out that the acid concentration in the stomach is closer to 0.1 Normal than 0.5 or 1.0 Normal.

The in vitro tests conducted by the Food and Drug Administration have shown no difference between 0.1 Normal and 1.0 Normal. Results of these tests are on file with the Hearing Clerk as part of the administrative record. However, these tests show that the increase in volume resulting from the use of 0.1 Normal complicates the test procedure because large pipets and burets would have to be used. Based on the Agency's findings, the normalities will remain the same. The increase in volume caused by the use of 0.1 Normal hydrochloric acid makes the test more cumbersome and awkward to conduct without a corresponding increase in accuracy.

31. There was comment that the pH meter should be calibrated between pH 1.1 and pH 7.0 instead of exactly at pH 4.0, because the calibration between 1 and 7 will allow for a more accurate determination of higher values. No data were submitted to support the statement.

The Commissioner has determined that calibration of the pH meter at 4.0 is sufficient to assure the accuracy of the test. Therefore, he will not change the calibration. The final order provides only for checking the operation of the meter at pH 1 since there is no need to calibrate the meter twice. The analyst need only calibrate the meter and then assure himself that it is operational at another pH, i.e., pH 1.

32. There were comments stating that the temperature should be controlled since it is the simplest of specifications and is used in most laboratory tests. The comment proposed that the test should be conducted at body temperature, 37° C.

The Commissioner agrees that this is a variable that can be eliminated and yet not complicate the test. However, during testing, the Food and Drug Administration has shown that there is no difference between 25° C and 37° C. It is more appropriate to use room temperature since it requires less equipment. The Commissioner has therefore, concluded that the temperature will be designated at 25° C±3° in the final order.

33. There was comment that the disintegration test should be altered for chewable tablets.

The Commissioner advises that, under § 331.1(b) (the disintegration test), the proposed disintegration test does not apply to chewable tablets. The Commissioner does not believe that a disintegration test for chewable tablets is necessary. It would be inappropriate to require a chewable tablet to disintegrate in the same manner as a swallowed tablet because the chewable tablet labeling instructs the consumer to reduce the particle size of the tablet. The disintegration test for a swallowed tablet is merely a test to assure that it be reduced to particle size on swallowing.

34. One comment stated that it is inappropriate to adopt a 10 minute standard for the disintegration of swallowed antacid tablets, because there is no substantial evidence to indicate that passing or failing the test will affect the tablet's safety or efficacy, nor are there any data indicating that the 10 minute test is correlated to in vivo results.

The Commissioner concludes that the position taken in this comment would allow the swallowed tablets to have any disintegration time or to use the United States Pharmacopeia standard of 30 minutes. The Panel in their recommendation concerning the in vitro test stated that, on the fasting stomach, a tablet that takes 30 minutes to dissolve probably would be ineffective because it would be gone from the stomach in half that time. Most of the antacid has left the stomach 15 minutes after ingestion. An undissolved tablet cannot be effective. The 10 minute standard should not create a hardship since it only requires that tablets that fail to pass the disintegration test must be labeled as chewable tablets so that the consumer will know that he must physically reduce the tablet size to get the benefit of the active ingredients.

35. There was comment that, if a tablet does not disintegrate in 10 minutes or less, the manufacturer should have the option of testing the whole tablet according to the preliminary antacid test. The comment contended that, if the whole tablet passes the preliminary test, the manufacturer may recommend swallowing on the label.

The Commissioner concludes that a tablet which fails to disintegrate and yet passes the preliminary antacid test is more properly handled through a new drug application or an amendment to the monograph. No data have been presented to explain why a tablet would fail to pass the disintegration test, and yet pass the in vitro test. If such a condition did exist, data to show in vivo effectiveness would need to be presented.

36. There were comments that the method of comminuting the tablets to pass through a number 20 U.S. mesh sieve would allow a person to finely powder the tablet. One comment provided data to show that cement, if finely powdered, would pass the in vitro test.

The Commissioner advises that the test was not designed to allow the use of a fine powder. For this reason a lower limit has been placed on the particle size in the final order, to prevent the comminuting of tablets to a fine powder.

37. There was comment that ethanol, when used as a wetting agent, may reduce the acid neutralizing capacity of a product.

The Commissioner concludes that, although ethanol may have an effect, it is not significant. The Commissioner has therefore decided to allow the discretionary use of ethanol as a wetting agent. Some comments have stated that particles float on the top of the test solution and the ethanol will reduce the surface tension and decrease the number of particles that float, but in Food and Drug Administration tests few products exhibited this tendency and it is doubtful that the use of ethanol will be required. The person conducting the test must determine if a wetting agent is necessary.

38. There was comment that the density and not the specific gravity should be used in testing liquid samples.

The Commissioner concludes that the comment is correct in that the proper designation for the calculation figure is density. The final order has been changed accordingly.

39. There was comment that, because the concentrated antacids would exceed the 30 milliequivalent titration, the procedure should allow for a greater number of milliequivalents to be used.

The Commissioner doubts that there are many antacids with neutralizing capacities greater than 30 milliequivalents. No data were presented to the Food and Drug Administration concerning such a product. Therefore the Commissioner believes that it is proper to provide for an exemption from the in vitro procedure for a stronger antacid, or an amendment to the test if necessary, upon the petition of a manufacturer.

40. There was comment that the United States Pharmacopeia XVIII simulated gastric fluid test solution contains enzymes which are not necessary for the test and increases its expense.

The cost of the enzymes would be approximately twenty cents per test, which is not significant. At the present time, however, there is no scientific justification for adding the enzymes other than the fact that they are present in the stomach. The Commissioner believes that future testing in this area should address itself to this issue. Until scientific evidence is forthcoming on why enzymes must be in the test solution, the Commissioner has concluded that the simulated gastric fluid test solution shall not contain enzymes. The final order has been modified accordingly.

41. There was comment that the stirring speed for the in vitro test should be eliminated because it has no direct reference to similar in vivo action.

Data submitted in response to the January tentative final monograph and some Food and Drug Administration testing showed that a test with no established stirring speed would allow a procedure that provides for an infinite number of results depending on the stirring speed. The test must be reproducible, and therefore a stirring speed must be identified.

42. There was a comment requesting an exemption for a product from the 10 minute time period required in the acid neutralizing capacity test contained in the November tentative final order.

The Commissioner stated at the hearing that a revised tentative final monograph acid neutralizing test was being published and that, if a deviation from that test was required, an exemption should be requested pursuant to § 331.29 (formerly § 130.305(a)(1)(iii) after the final order was published.

43. There was comment that the in vitro test should be validated by appropriate bodies.

The Commissioner has had the test reviewed and validated by Food and Drug Administration laboratories and has determined that it is valid. The validation studies have been filed with the Hearing Clerk.

ACTIVE INGREDIENTS

44. There was comment that bismuth salts protect the mucous membranes of the stomach and duodenum and that they should be allowed to be used in combination with other antacids.

Bismuth salts are included in the monograph as active ingredients with potential acid-neutralizing properties and can be used in a combination as long as they contribute 25 percent of the total acid neutralizing capacity of an antacid product. Based on the fact that no data were submitted to prove that bismuth salts are effective as protectants to the mucosal membrances, the Commissioner does not recognize the bismuth salts as having been proved effective for such purposes. Data would have to be presented to demonstrate effectiveness for this particular use to allow such a labeling claim.

45. There was comment that an exemption should be provided from § 330.1(g) (formerly § 130.302(g)) for sodium bicarbonate powder. The powder is used as a food product, tooth cleanser, and mouth wash, as well as an antacid, and therefore an accidental overdose warning appearing in § 330.1(g) (formerly § 130.302(g)) is inappropriate because of the nature of the product.

The Commissioner recognizes the many uses of sodium bicarbonate (baking soda) as a food and for various other purposes. The Commissioner therefore believes that it would be proper to exempt sodium bicarbonate powder from the general accidental overdose warning contained in § 330.1(g) (formerly § 130.302(g)) because of its extremely low potential for injury from an overdose. The product labeling must, however, fully comply with the antacid monograph, including directions for use, all applicable warnings, etc.

INDICATIONS

46. There was comment that the words "upset stomach" should be included in Category I.

The Commissioner considered this issue in detail in paragraph 49 of the preamble to the tentative final order and no new data or information were presented to support a change in that decision. Accordingly, no change has been made in the monograph with respect to this matter.

47. There was comment that justification for the term "upset stomach" should not require clinical trials to establish a relationship between consumer language and acidity.

A clinical trial to establish a relationship between what consumers regard as "upset stomach" symptoms and OTC antacid drugs would be an appropriate approach to justify this claim. Another valid approach to justify approval of use of the claim "upset stomach" for an antacid is a statistically valid consumer survey to determine how the consumer interprets the term "upset stomach". The Commissioner's present conclusion that the term "upset stomach" has not been justified is based on the fact that this phrase is used by consumers to describe the symptoms relieved by completely different products. Paragraph 49 of the preamble to the tentative final order discussed a marketing study where this phrase was applied by consumers to five products, only two of which were simple antacids.

It would not be sufficient to show a particular product which uses this claim to consumers and to ask for what symptoms it should be used. The question is what the phrase means to the consumer, not what words does the consumer think of to describe an advertised brand name product or a class of products.

DIRECTIONS FOR USE

48. There were comments to the effect that the term "as needed" should be used to describe dosage in antacid labeling instead of labeling requiring a specific dosage schedule by time interval or time period. It was further proposed that no other directions for use would be needed since the warning would express the maximum dose.

The Commissioner concludes that the directions for use in antacid labeling properly indicate the specific dosage and time periods for which the product is recommended. It would be improper to recommend that any antacid be used "as needed," since this would promote unrestricted use.

The Commissioner has also concluded that the proposed phrase "except on the advice and supervision of a physician" is confusing, and that it should be revised to read "or as directed by a physician."

WARNINGS

49. There were comments that § 331.30(b) (formerly § 130.305(c)) and § 330.1(g) and (i) (formerly § 130.302 (g) and (i)) contain warning statements which a manufacturer should be able to consolidate and simplify. There was also a request that, when a manufacturer develops warning statements, they be submitted to the Food and Drug Administration with an understanding that the statement is approved unless the manufacturer is otherwise notified.

The Commissioner agrees that there may be certain products that would require more than one of the warnings specified, and that clearer labeling may be provided by consolidating such statements. The Commissioner has decided that any two or more warning statements may be combined provided that the resulting statement uses all of the specific words contained in the monograph in the order specified, and provides a clear and readable warning which the consumer can understand. This will permit deletion of duplicative phrases without losing uniformity in warning terminology. Thus, the warnings in § 331.30(b)(4) and (5) may properly be combined to read "Do not use this product except under the advice and supervison of a physician if you have kidney disease or if you are on a sodium restricted diet," since none of the operative words or phrases are eliminated or rearranged. If

any manufacturer is concerned about a combination of warnings he intends to use, he is encouraged to submit it to the Bureau of Drugs for review and comment.

50. There was comment that the language used in a warning should not be mandatory because the manufacturer may use minor variations in words which would allow clearer understanding by consumers.

The Commissioner believes that uniformity in labeling language is essential to consumers. For this reason, the combining of warnings is permitted only where it will retain uniform terminology. Allowing minor word variations, or rearrangement of the same words, would result in dissimilar or confusing warnings which would not be in the best interest of the public. The Commissioner has also included in the final monograph standard headings for the labeling sections on warnings, drug interaction precautions, and directions, to promote such labeling uniformity. However, the Commissioner recognizes there may be circumstances where warnings can be improved. A manufacturer may seek an amendment to the monograph if he concludes that a warning or other labeling should be revised.

51. There was comment that including the phrase "except under the advice and supervision of a physician" should not be required to appear in both the maximum dosage statement and any additional warnings, since this would be duplicative.

The Commissioner concludes that the consolidation of warnings discussed in paragraph 49 of this preamble will permit a manufacturer to eliminate duplication of common phrases in warning statements.

52. There was comment that two of the warning statements name specific diseases and that physicians do not always inform a patient of his specific disease condition. The comment suggested that, because the patient may not know his disease, the labeling should warn against consumption of additional quantities of the active ingredients involved (i.e., potassium and magnesium) rather than against use of the OTC drug in specific disease conditions. There were no data submitted to support this comment.

The Commissioner concludes that, although the monograph necessarily determines the safety and effectiveness of antacid drug products in terms of their active ingredients, consumers are more likely to be told and to remember their disease conditions than a list of prohibited chemical ingredients. No data were submitted to show that physicians ordinarily provide a list of prohibited ingredients to patients that would allow them to use such labeling, or in any event that physicians are more likely to do this than to inform the patient of his disease. Under § 330.10(a)(3)(v) (formerly § 130.301(a)(3)(v)), labeling must be likely to be read and understood by the ordinary individual including the individual of low comprehension. The Commissioner concludes that this labeling meets that requirement.

53. There were numerous comments that the 5 percent level which determines whether a warning is necessary relating to constipation and laxation in § 331.30(b) and (c) (formerly § 130.305(c)(2) and (3)) is arbitrary and incapable of scientific validation.

The Commissioner concludes that any manufacturer is capable of conducting a well-controlled clinical study on the maximum recommended dose to determine whether it causes laxation in more than 5 percent of the users, and thus that scientific verification is entirely reasonable. If more than 5 percent of the users of an OTC antacid are suffering from constipation or laxation, that is a significant fact which merits a warning, because antacids are often used by the adult population, many of whom already have irregular bowel habits or other gastrointestinal problems. Many antacids are also recommended by physicians at much higher dosages than those appearing on the label, and such a warning would be important to inform the consumer that he may experience bowel irregularity.

54. There were also comments that the 5 percent level is unreasonable because OTC medications are intended for use only for a short period of time and therefore significant constipation or laxation is unlikely.

The Commissioner concludes that it is important that the manufacturer be required to demonstrate that laxation or constipation is unlikely. If in fact it is unlikely, the required test will demonstrate this fact and the warning will be inapplicable.

55. One comment stated that the 5 percent rule could result in labeling for a product indicating that it could cause both constipation and laxation in a patient population because different people react differently to the same ingredient. It was proposed that the 5 percent cut-off level be raised to 15 percent to identify the effect more clearly.

The Commissioner concludes that if a product is capable of causing both effects at the maximum daily dose in 5 percent of the patient population such information should properly be provided to the consumer in the label. No data were presented to show that any such product exists. The Commissioner rejects the proposed 15 percent cut-off level because these products are often used by people greatly in excess of the amount recommended in the label and because consumers should be alerted to any significant side effect that will affect a substantial number of users. No justification was provided for the proposed 15 percent cut-off level.

56. There was comment that the provisions relating to the warnings required by § 331.30(b)(4)) formerly § 130.301(c)(4)) when the magnesium level exceeds 50 milliequivalents a day should be revised to state that they are applicable only where the level exceeds 150 milliequivalents per day.

The summary minutes for the early meetings of the Antacid Panel reveal that the Panel initially considered 150 milliequivalents per day of magnesium as the level for requiring a warning. However, upon reconsideration the Panel reduced the amount to 50 milliequivalents because of the following considerations. The normal individual consumes from 20 to 40 mEq of magnesium per day and about one third of that is absorbed into the body. If a consumer is taking a magnesium-containing antacid, anywhere from 15 to 30 percent of that magnesium is absorbed. If a person does not have normal renal function it is possible to have hypermagnesmia toxicity, i.e. the level of magnesuim in the body may reach a toxic level.

The Commissioner agrees fully with the Panel's reasoning and therefore finds the warning for 50 mg. is appropriate. The primary target population for antacids is adults, many of whom suffer from kidney problems or take doses larger than those recommended in labeling. Therefore the safety factor becomes significant. The normal individual with no renal problem can easily tolerate 150 mg. of magnesium a day, but for a patient who has renal failure large doses of an antacid could present a serious problem that is avoidable by the warning contained in the final order.

57. One comment stated that it is appropriate to provide information on the salt content for an antacid, but that the more appropriate approach would be to label the product as "low in sodium" when the product contains less than 5 milliequivalents in the recommended dose. The comment recommended removal of the warning statement required on a product containing greater than 5 milliequivalents of sodium in the recommended dose.

The Commissioner is concerned that a statement "low in sodium" might be read by consumers as a claim that the product has advantages in relation to other antacids, which in fact may not be true. Such labeling would also remove the sodium warning from high sodium-containing products and thus fails to designate products that are not appropriate for a sodium-restricted diet. For these reasons, the Commissioner concludes that it is more appropriate to require the sodium warning and thus allow the doctor and patient to review whether a product containing more than 5 milliequivalents of sodium is appropriate for use.

58. There were comments that the Food and Drug Administration has ignored the drug interaction warnings required in prescription drug package inserts and some of the more recent scientific literature. There was specific comment that aluminum ingredients interfere with the absorption of tetracycline.

The Commissioner has reviewed the literature citations contained in Evaluations of Drug Interactions, 1973, the Antacid Panel Report, and the package insert labeling for prescription drugs. He concludes that there is adequate scientific evidence that the aluminum compounds may interfere with tetracycline and that a drug interaction warning statement should be required on the label.

The Commissioner concludes that it is important that consumers understand the basis for this warning. Accordingly, the final monograph has been revised to require that this information be contained in a separate labeling section headed "Drug Interaction Precautions." This will advise consumers of the reason why these two types of products should not be used concurrently. The manufacturer is, of course, also free to add additional explanatory information to the effect that use of the product may prevent the proper absorption of tetracycline.

PROFESSIONAL LABELING

59. A number of comments requested that the acid neutralizing capacity be removed from the labeling for health professionals (§ 331.31(a)(1)) (formerly § 130.305(f)(1)) because the acid neutralizing test has undergone numerous changes and may not correlate with in vivo results.

For the reasons already summarized above, the Commissioner believes that the in vitro test is an excellent means of determining effectiveness, which closely correlates with in vivo results. Nevertheless, the Commissioner is concerned that confusion could occur in the near future if the acid neutralizing capacity were required to be in professional labeling, because of required reformulations and efforts to find an improved in vitro or in vivo standard. The Commissioner has therefore concluded that manufacturers will not be required to state the acid neutralizing capacity in professional labeling until 2 years from the effective date of the monograph. This will give industry an opportunity to conduct all necessary tests and to propose an improved in vitro test or an in vivo test with even greater reliability.

COMBINATIONS WITH NONANTACID ACTIVE INGREDIENTS

60. There was comment that alginic acid is effective for the treatment of reflux esophagitis. An article by McHardy, G. and L. Balart, "Reflux Esophagitis in the Elderly, with Special Reference to Antacid Therapy", American Geriatrics Society, 20: 293, 1972 concerning a summary of 100 patient case reports was cited as support for this comment.

The Commissioner notes that even the comment admits that alginic acid is not a potent antacid and that its unusual characteristic of floating is the factor that may aid in the management of patients with esophagitis. The Commissioner rejected this comment in paragraph 25 of the preamble to the tentative final order, and no significant new or additional data or information have been submitted. This ingredient is not sufficiently effective to meet, by itself, the requirements for effectiveness set out in the final order. The problem continues to be that no well controlled studies have been submitted demonstrating that alginic acid is otherwise clinically effective in combination with an effective antacid. Until such studies are available, alginic acid will not be included in the antacid monograph.

61. Another comment supporting the use of alginic acid as a Category I ingredient took exception to the findings of the Commissioner in paragraph 25 of the tentative final order. First, it was stated that, as long as a study shows that an antacid/alginic acid combination has the same effectiveness as an antacid alone in treating regurgitation and epigastric gas, the combination product should be approved. Second, the comment argued that there is incontrovertible evidence that the alginic acid floats. Third, it was proposed that the concern of the Antacid Panel about the effectiveness of the product when a patient is in a reclining position can be eliminated by including in the labeling directions a caution statement stating that the user should not recline. Fourth, there was comment that an additional study by Grossman, A. E., et al., "Reflux Esophagitis, a Comparison of Old and New Medical Management", Journal of the Kansas Medical Society, 74: 423–424, 1973, shows that the combination is equivalent to the standard antacid in relieving regurgitation and epigastric gas.

The first point deals with a study in which the antacid/alginic acid combination product shows little difference from the antacid alone. Pursuant to § 330.10(a)(4)(iv) (formerly § 130.301(a)(4)(iv)), the use of an active ingredient, alginic acid, in a combination drug must be shown to contribute to the effect of the product, i.e., the combination must result in a more effective product than the antacid alone. The alginic acid has no acid neutralizing capacity, and the referenced study clearly does not show that the alginic acid/antacid combination is more effective than an antacid alone or that alginic acid contributes to the claimed alleviation of symptoms. Thus, the available data fail to provide adequate evidence that alginic acid contributes to the effectiveness of the product.

The second point deals with whether floating, by itself, constitutes effectiveness. No scientific evidence has been submitted to show that floating is in any way related to clinical effectiveness, and in view of the study showing a lack of clinical effectiveness of alginic acid it is doubtful whether such proof can be obtained.

The third point referred to the fact that reclining may reduce the effectiveness of a floating product. The Commissioner concludes that consideration of any proposed warning or other labeling is properly deferred until studies are conducted to determine the clinical effectiveness of a floating alginic acid/antacid combination drug and its relationship to the position of the patient.

There is no indication in the article that the subjects were assigned so as to eliminate bias nor to assume comparability in the test group and control of pertinent variables such as duration of disease, age and sex. The most critical issue was the failure to minimize bias on the part of the subject and observer because the control in the study was a commercially available antacid that had different ingredients and would be easily distinguishable by the subject and the dispensing health professional. There is no indication that any effort was made to blind the study. The method of evaluation is explained but it was subjective in all subjects unless they had shown esophagitis in the initial esophagoscopy. Only one-half the patient population had shown esophagitis and both the antacid and antacid/alginic acid group showed objective improvement in esophagitis at the end of the one month study period. The study had attempted to measure four parameters: (1) Epigastric to retrosternal distress, (2) regurgitation, (3) epigastric gas and (4) motor symptoms of swallowing. The statistical analysis according to the investigators showed no significant difference in three out of the four comparisons between the antacid and the antacid/alginic acid product. The investigators also noted that the frequency of antacid administration used in the study may not have been adequate to produce therapeutic response in all patients. The investigators also concluded that the antacid/alginic acid combination "may" be beneficial in patients with retrosternal or epigastric gas. As indicated above, the article reporting the study does not meet a number of requirements of § 314.111(a)(5) (formerly § 130.12(a)(5)). The study does not answer the question whether alginic acid is effective alone or in combination in the treatment of retrosternal or epigastric distress. Until well-controlled studies are conducted in accordance with § 314.111(a)(5) (formerly § 130.13(a)(5)) to show clinical effectiveness, it will not be possible for the Commissioner to include this ingredient in the monograph.

62. There was comment that the use of a product containing an antacid and a salicylate for gastrointestinal symptoms, even if accompanied by pain symptoms, is not safe. To support the position, material previously provided as a comment on the proposal was resubmitted.

The Commissioner discussed this material in paragraphs 62 through 66 of the preamble to the tentative final order. No additional data of information were submitted. The Commissioner therefore reiterates the conclusions stated on this matter in the tentative final order.

The Commissioner notes that all of the evidence of safety of an analgesic/antacid combination drug is derived from studies and experience with products intended for administration in solution. Accordingly, the monograph has been modified to limit this combination to this type of product.

63. There was comment that the Commissioner in paragraph 66 of the preamble to the tentative final order had failed to evaluate properly an unpublished study on an antacid/analgesic combination. The comment stated that the Commissioner erred when he concluded that there was no statistically significant increase of blood loss, that the blood loss was not clinically significant, and that the bleeding resulting from an analgesic/antacid drug response normally continues for the duration of the treatment period. The comment

stated that, based on the incorrect evaluation of this study, the Commissioner's conclusion should be reversed.

The Commissioner has again reviewed this matter and has determined that his evaluation of the deficiencies in the study cited in this comment are correctly explained in paragraph 66 of the preamble to the tentative final order. First, the statistical significance of the differences in bleeding shown in that study is in dispute, and in any event is not the important issue. The important question bearing on safety is the medical significance of the amount of bleeding shown in the study. Second, the amount of blood loss shown is not clinically significant (Matsumoto, K. K. and M. I. Grossman, "Quantitive Measurement of Gastrointestinal Blood Loss During Ingestion of Aspirin," Proceedings of the Society for Experimental Biology and Medicine, 102: 517–519, 1959) and is within the range of blood loss found in normal individuals (Danhof, I. E., "Blood Loss from the Gastrointestinal Tract I. Normal Occult Loss," Bulletin of the Medical Staff of the Methodist Hospital of Dallas, 5: 35–38, 1972). Third, although a patient with pathological gastrointestinal lesions caused by cancer or ulcers bleeds irregularly and at widely varying times from day to day, the available evidence supports the conclusion that the blood loss caused in normal individuals by salicylate is continuous. (Croft, D. N. and P. H. N. Wood, "Gastric Mucosa and Susceptibility to Occult Gastrointestinal Bleeding Caused by Aspirin," British Medical Journal I, 137–141, 1967). Fourth, the single study on which the comment relies is not supported by substantial other well-controlled studies contained in the record. Fifth, the record does not contain any significant number of case histories of such acute bleeding caused by this widely marketed type of product consumed in large quantities by a substantial body of the public for many years. If a significant medical problem existed it would be expected to have been reported by now.

64. One comment stated that the Food and Drug Administration has misinterpreted the OTC combination drug policy as to an antacid/analgesic combination, because the policy requires that each ingredient contribute to each effect. The comment contended that each ingredient in the antacid/analgesic combination would need to be shown to contribute to both effects, e.g., the antacid ingredient would also need to be effective for a headache.

The Commissioner advises that the comment misinterprets the plain meaning of the OTC combination policy contained in § 330.10(a)(4)(iv) (formerly § 130.301(a)(4)(iv)) and explained in paragraphs 63–66 of the preamble to the final regulations establishing the procedures for the OTC drug review published in the FEDERAL REGISTER of May 11, 1972 (37 FR 9664). The policy states that each active ingredient must make a contribution to the effect claimed for it, and not that each active ingredient must contribute to all effects claimed for the product. To adopt the approach suggested by the comment would require removal of all dual purpose combination drugs from the market because rational concurrent therapy could only be found where all the ingredients had the same effects. The Commissioner states that this was not the intent of the regulation and that such a policy would be unreasonable from a medical standpoint.

One person who opposed the combination as irrational stated at the public hearing that he would concurrently prescribe an analgesic and an antacid for a patient who exhibited the concurrent symptoms of acid indigestion and headache. He stated, however, that he would prescribe an analgesic other than a salicylate, and also expressed concern about the fixed dosage contained in existing antacid/analgesic combinations.

The Commissioner concludes that this comment supports his determination that an antacid/analgesic combination constitutes rational concurrent therapy. Symptoms justifying use of these drugs often occur concurrently. The combination of these drugs meets each requirement of § 330.10(a)(4)(iv) (formerly § 130.301(a)(4)(iv)). The antacid monograph determines the effective dose for the antacid component of this combination, and the internal analgesic monograph will determine the effectiveness dose for the analgesic component. Thus, the fixed combination will be within the effective dosage range for both ingredients when administered concurrently according to the label directions for use.

The Commissioner notes that the safety of analgesic ingredients is currently being reviewed by the Internal Analgesic Panel. The final antacid monograph provides that any safe and effective analgesic, as determined by the internal analgesic monograph, may be used in combination with an antacid for concurrent analgesic and antacid symptoms. Accordingly, the safety, effectiveness, and appropriate labeling of the analgesic component of an antacid/analgesic combination remains under consideration at this time, and will be the subject of a further review and determination by the Commissioner in accordance with the procedures specified in § 330.10 (formerly § 130.301).

65. There was comment that the dosages of the active ingredients in an analgesic/antacid combination would be irrational because of an insufficient amount of antacid or analgesic. The comment states that the combination provides about one-fourth of the antacid needed in treating ulcers or hypersecretion.

The dosage of antacid contained in the combination product must meet the antacid in vitro test which has been designated as the standard of effectiveness for an OTC antacid. The Commissioner has determined that the combination antacid/analgesic is not appropriate for peptic ulcer therapy and under the final monograph it cannot lawfully be promoted for antacid use alone. Moreover, consumer labeling may not lawfully promote any antacid for peptic ulcer therapy under the final monograph. Accordingly, this comment raises issues based on an incorrect interpretation of the monograph.

66. There was comment that banning combinations for the concurrent symptoms of constipation and acid indigestion and yet approving those for the concurrent symptoms of acid indigestion and headache was irrational.

The Commissioner concludes that there is a significant target population that suffers from acid indigestion and headache at the same time. There was no information submitted to indicate that this is true with acid indigestion and constipation.

67. One comment stated that an antacid/analgesic combination should not be used only as an antacid, citing the Medical Letter, 15: 36, April 13, 1973.

The Commissioner concurs, and the labeling for the combination required in the proposal, the tentative final order, and the final order clearly so states.

68. There was comment at the hearing that the response to a questionnaire mailed to 275 gastroenterologists showed that 44 percent replied indicating that an antacid/analgesic (salicylate) combination was irrational.

The Commissioner concludes that the flaws in this mail survey make the results unreliable and irrelevant to the issues being considered. First, the mail survey used an obviously biased questionnaire. The questionnare set out quotations from the report of the Antacid Panel that were incomplete and taken out of context and thus presented an incomplete picture. The results must therefore be disregarded as unacceptable evidence on which to base any decision. Second, the mail survey did not include the requirements for a combination drug set out in § 330.10(a)(4)(iv) (formerly § 130.301(a)(4)(iv)) of the regulations. Accordingly, there was no standard against which to judge the appropriateness of the combination involved. Third, the mail survey included no scientific data on which the respondents might base an opinion. The information available to the Commissioner in the administrative record of this proceeding does not indicate that any of the respondents based their conclusions upon scientific evidence. Fourth, the mail survey did not ask whether any of the respondents had observed gastrointestinal bleeding that had been proved to be causally related to an antacid/analgesic combination drug. The information available to the Commissioner in the administrative record of this proceeding does not indicate that any of the respondents stated that they had found any such situation. Fifth, the courts have ruled that the opinions and anecdotal views of physicians are an insufficient basis for a decision that a combination drug meets the legal and scientific requirements of the Federal Food, Drug, and Cosmetic Act. See Upjohn Company v. Finch, 422 F. 2d 944 (6th Cir. 1970) and Weinberger v. Hynson, Westcott and Dunning, 412 U.S. 609 (1973). This principle applies regardless whether the phy-

sicians may approve or disapprove of a particular combination drug. Unsubstantiated opinion is no substitute for well-grounded scientific evidence. Sixth, the mail questionnaire focused upon a particular brand of a marketed product rather than upon a request for scientific evidence relating to a type of combination drug. This reference introduced further subjective factors into the response, relating to the labeling and advertising for the particular brand product mentioned, unrelated to the scientific and medical issues involved. Accordingly, the Commissioner concludes that this mail survey is entitled to little or no weight with respect to this matter.

69. One comment objected to comments made to the Antacid Panel by the Assistant General Counsel, Food and Drug Division, Department of HEW, and to the participation of the Assistant General Counsel in this matter because, prior to his government employment, he had provided legal advice to a client who had manufactured an antacid/analgesic combination drug.

The Commissioner has thoroughly reviewed this matter and has concluded that no impropriety has occurred. The Assistant General Counsel has stated that he had not advised the company involved on any of the issues involved in the OTC Review and that he has followed the guidelines for disqualification which he established in testimony before the Senate Committee on Commerce on September 17, 1971, which exceed the requirements of the law. A copy of that testimony has been included as part of the administrative record of this proceeding.

Moreover, the Commissioner reiterates that the decision on both the tentative final order and this final order with respect to the antacid/analgesic combination involves medical and scientific issues for which he is responsible, and not legal issues. The Commissioner advises that, in considering the status of the combination, his decision has been based upon sound scientific evidence and reasoning rather than upon theoretical possibilities, particularly in light of the long marketing history of this type of product without any significant reported safety problem. The criteria for a combination drug are established in § 330.10 (a)(4)(iv) (formerly § 130.301(a)(4)(iv)) of the regulations in readily-understandable terms, and the Commissioner has applied those criteria as they are written. The Commissioner and his medical advisers have reviewed the administrative record in this proceeding, and the Commissioner personally presided over the public hearing at which the status of an analgesic/antacid combination drug was a major issue. Thus, full responsibility for the decision on this matter rests with the Commissioner, and not with the Assistant General Counsel, the Antacid Panel, or any other persons.

70. There was comment that the population to which the antacid/analgesic combination is directed contains a large number of individuals who are at an increased risk from salicylates because of underlying diseases. The comment conceded that an analgesic and antacid would be appropriate treatment for a person with hyperacidity and headache.

The Commissioner concurs with the comment that an antacid and an analgesic given concurrently would be the drugs of choice for a person with hyperacidity and headache. The Commissioner concludes that the data submitted support a fixed dosage combination for OTC use for this purpose and that in fact for many people the combination may be safer than taking the individual ingredients separately. There is some evidence that whatever harmful effect may result from salicylate may be reduced by buffering it with an antacid ingredient. Such a protective effect could not occur unless ingestion is at least simultaneous and may not occur without prior admixture. The Internal Analgesic Panel is considering appropriate labeling for analgesic ingredients, including whether warnings may be appropriate for salicylates to prevent use in situations where it could be harmful.

71. There was comment that, where there is inclusion of a salicylate, a warning statement concerning peptic ulcer would be appropriate on the antacid/analgesic combination.

The Commissioner will not comment on this issue at this time because the Internal Analgesic Panel is considering appropriate labeling for analgesic ingredients. As already noted above, the Commissioner will address this issue in the course of reviewing that Panel's recommendations.

72. There was comment that the finding that an antacid/analgesic combination is irrational for antacid use alone should not apply where sodium acetylsalicylate is used in a highly buffered solution.

This matter was fully considered in paragraph 64 of the preamble to the November tentative final order. To accept this comment would be to allow the use of a salicylate in a product that is represented only for antacid use. Until adequate and well-controlled studies are presented to show that a salicylate is effective for relief of upper gastrointestinal symptoms, it would be misleading for a product to represent that a salicylate is useful for relief of acid indigestion or other symptoms for which antacids are effective.

73. There was comment that data had been presented to show that sodium acetylsalicylate in a highly buffered solution is beneficial in the relief of symptoms of upper gastrointestinal discomfort. The comment stated that the acetylsalicylate has a therapeutic effect on the inflamed gastrointestinal tissue, and that if more data are needed the ingredient should be placed in Category III while the data are being collected. The data submitted were derived from experiments in laboratory animals. They included studies showing that aspirin lessened experimental peritonitis in the mouse and rat in addition to a study in cats. These studies indicate that aspirin may have an anti-inflammatory effect in the viscera. The comment stated that additional evidence conclusively establishing the precise role which acetylsalicylates play in the relief of upper gastrointestinal symptoms will require further development in methodology.

The Commissioner concludes that this data base, limited to studies in laboratory animals, is not adequate evidence to allow the use of an antacid claim for a salicylate or to justify continued marketing for this use pending further testing. There are also other data which indicate that salicylates may cause gastrointestinal bleeding. It may well be that the dosage and method of administration determine the effect a salicylate will have, but until well controlled studies can adequately resolve the issue the Commissioner concludes that a product containing a salicylate may not be labeled for antacid use alone.

74. There was comment that the antacid monograph in § 331.30(g)(3) (formerly § 130.305(g)(3)) failed to recognize professional labeling for antacid/antiflatulent combinations.

The comment is correct. A new provision has been added to § 331.31(b) stating that an antacid/antiflatulent combination may contain the professional labeling allowed for antacids and antiflatulents, i.e., peptic ulcer and postoperative gas pain.

75. There was comment that the inactive ingredient(s) should be listed on OTC drug labels.

The Commissioner reiterates the conclusion stated in paragraph 28 of the preamble to the tentative final order that the issue of listing inactive ingredients on OTC labels would be considered by the National Drug Advisory Committee. This matter is inappropriate as a subject matter for the individual OTC monographs. The Federal Food, Drug, and Cosmetic Act does not presently permit the Food and Drug Administration to require the labeling of all inactive ingredients.

ANTIFLATULENT

76. There was comment that it was inappropriate to create an antiflatulent monograph in the tentative final order and that a new call for data should have been published.

The Commissioner is of the opinion that it was proper to consider the status of the ingredient simethicone since the record before him fully addressed the issue and opportunity for comment and a public hearing on the matter were provided. Paragraph 67 of the preamble to the tentative final order stated that any other ingredient for consideration as an antiflatulent should be submitted to the Miscellaneous Internal Panel.

77. There was comment objecting to the limitation of antacid products containing simethicone to a use solely for concurrent symptoms of gas associated with heartburn, sour stomach or acid indigestion. The comment requested that the monograph allow an antacid claim alone, even though the product also contains the antiflatulent ingredient. This comment was based on the view that both

ingredients have their effect on the same organ system for relief of related or often indistinguishable symptoms.

The Commissioner notes that this comment raises the issues of what is a combination drug and how it shall be labeled. Section 330.10(a)(4)(iv) of the regulations states that an OTC product may combine two or more safe and effective active ingredients when each active ingredient makes a contribution to the claimed effect(s). Simethicone combined with an antacid has been adjudged safe and effective. Each makes a contribution to the product's effects, but each ingredient is pharmacologically different in that each has a different mode and method of action. The antacid reduces the acid level of the stomach. The simethicone reduces the surface tension of the bubbles that are present in the stomach allowing them to break up or create a larger gas mass which is more easily expelled from the gastrointestinal tract, a mechanism of action that is wholly different from that of the antacid. Since each of these ingredients has an independent pharmacologic action of its own, they are each marketed commercially as single ingredients.

Section 330.10(a)(4)(iv) of the regulations also states that a combination drug shall bear adequate directions for use and provide rational concurrent therapy for a significant proportion of the target population. In paragraph 63 of the preamble to the final procedural regulations published in the FEDERAL REGISTER of May 11, 1972 (37 FR 9464) the explanation was made that "There is no sound medical or scientific reason to have an active ingredient in a combination unless it makes a contribution to the claimed effect." In this case simethicone reduces the gas and the antacid reduces the acid level of the stomach contents. Thus, the target population for the combination product must be those who have acid indigestion, sour stomach, heartburn and gas. Otherwise, both ingredients would not be necessary. For gas alone, simethicone would be sufficient; and for acid indigestion alone, an antacid would be sufficient.

Section 330.1(a)(4)(v) of the regulations states that the "Labeling shall be clear and truthful in all respects and may not be false and misleading in any particular. It shall state the intended uses and results of the product . . ." Here, the combination is useful if the consumer has both conditions, acid indigestion and gas. Failure to include both conditions on the label of the product would result in a label that was not clear and truthful. If the consumer has no gas, he is not part of the target population for which the combination is intended. Failure to include both indications would mean that the label would not inform the consumer of the results he could expect, relief from acid indigestion and gas.

The comment contends that many consumers have the need for the antacid and antiflatulent together and do not realize that both symptoms are present, and that for this reason the product need only be labeled as an antacid. No data were presented to support the comment. The sole basis for the comment is the fact that the combination product has been marketed as an antacid for years and simethicone has a wide margin of safety. The purpose of the OTC drug review is to evaluate the safety and effectiveness and labeling of OTC drug products on the basis of scientific evidence, so that consumers will be able to make more rationale OTC drug purchases. An underlying premise of the OTC drug review, and, indeed, of the sale of drugs over-the-counter rather than on prescription, is that the consumer is capable of making an intelligent choice of a drug product if he posseses adequate information about the products offered for treatment of specific conditions or symptoms. To omit the effects of an active ingredient from the label is inconsistent with that premise and defeats the very purpose for which the OTC drug review has been undertaken.

The Commissioner notes that a related question has been raised concerning the limitation to be placed on the combination product containing antacid and analgesic ingredients. There the view has been expressed that the combination should not be permitted because it is not rational therapy for an individual who has a condition for which the antacid alone is appropriate treatment. The Commissioner agrees with that view, but has concluded that labeling which clearly indicates that the combination is to be used only when concurrent symptoms of acid indigestion and headache are present is sufficient to enable the consumer to exercise a reasoned judgment as to the appropriateness of the combination. Accordingly, a combination antacid-analgesic product must be indicated in its labeling and promotion for use solely for the concurrent symptoms of headache and acid indigestion. Section 331.15 (b) [formerly § 130.305(g)(2)].

The Commissioner sees no basis for reaching a different result with respect to a combination of antacid and antiflatulent ingredients. That the concurrent symptoms which that combination is intended to treat affect the same organ system rather than different systems does not argue in favor of labeling which fails to indicate what is the fact, that the combination is intended as therapy for two distinct conditions of that one system. Similarly, that some consumers may be unaware that their discomfort is caused by both gas and acid indigestion rather than just by acid indigestion is not a cogent reason for labeling the combination only as an antacid any more than it is a valid basis for representing the drug solely as an antiflatulent. There is no evidence that consumers universally, or even generally, assume that the discomfort associated with gas and acid indigestion together is caused by acid indigestion alone, so that promoting the combination exclusively as an antacid would at least provide sufficient information to those suffering from those two concurrent symptoms to enable them to purchase a product intended to treat them both. Even if there were such evidence, there would still be no acceptable reasons for allowing convenience or marketing considerations to prevail over the objective of clear and truthful labeling by not advising the consumer that the product is in fact intended to treat two conditions. Finally, the contention that simethicone may not be harmful to one who does not need it does not support the desired result of not openly informing the consumer of the purpose of a drug to treat a condition or symptom which the consumer may not have. The goal of clear and truthful labeling of OTC drugs is not limited to those situations where it is necessary to avoid adverse consequences. The consumer should always be informed of the purpose of an OTC drug so that he can make up his own mind to the extent that his knowledge permits. His freedom of choice should not be qualified because the manufacturer assumes that some consumers lack adequate knowledge, or because, in the manufacturer's opinion, the choice is unimportant.

Based on these considerations, the Commissioner concludes that an antacid/antiflatulent combination must contain both indications.

78. There was comment that the maximum daily dose of simethicone established in the antiflatulent monograph in the tentative final order is too low and that there are data available showing usage at much higher dosages under the supervision of a physician.

The Commissioner concurs that the dosage used by physicians has exceeded 500 milligrams, but points out that there are no data on OTC use of this ingredient at higher dosages. Because of the complete lack of data concerning higher OTC dosages the Commissioner has decided that the daily dose for OTC use will be set at 500 milligrams at this time and that there will be no dosage limitation on professional labeling. If data are presented at the Miscellaneous Internal Panel to justify changing these dosages, appropriate changes will be made.

79. There was comment that § 332.30 (a) (formerly § 130.306(b)) improperly allows the manufacturer to use all commonly existing descriptive terms such as bloating, flatulence, colic, belching, etc. to describe an antiflatulent.

The Commissioner advises that this is an erroneous interpretation of the monograph. The monograph is not intended to allow the use of such words as bloating, colic, belching, etc. The monograph allows use only of the word "antiflatulent" or the statement "to alleviate or relieve symptoms of gas." Those are the only terms that can properly be used for OTC antiflatulent drugs.

80. There was comment that endoscopic and radioscopic examinations should be added to the professional labeling indications for OTC antiflatulent drugs.

The Commissioner agrees that it is appropriate to add endoscopy as an indication but concludes that there are insufficient data to support a radiologic

indication at this time. Data on the latter indication may be submitted to the Internal Miscellaneous Panel and will be considered as part of that proceeding.

81. There was comment that § 332.15 (formerly § 130.306(e)) does not provide for labeling for health professionals.

The Commissioner concurs, and a clarifying sentence has been added as § 332.31 (b).

EFFECTIVE DATE OF MONOGRAPH

82. There were a number of comments requesting an extension of the effective date of the final monograph beyond the 6 months indicated in the proposal, because of the shortages that exist in packaging material and the energy situation as it affects the OTC drug industry. In support of these comments, data have been submitted from 15 companies concerning their ability of relabel and reformulate. The comments requested that, for products where no reformulation is necessary, the product labeling ordered by the manufacturer 6 months after the effective date would be in compliance, and for those products where reformulation is necessary, all labeling ordered 18 months after the effective date would be in compliance.

After reviewing the data and considering the comments the Commissioner concludes that it is reasonable to establish the following conditions for the effective date of the final monograph. The effective date of the monograph will be July 5, 1974, with the following exceptions. The effective date for all labeling for products not receiving an extension of the effective date for reformulation shall be June 5, 1975. Where reformulation is necessary, and if sufficient data and reasons are supplied, the Commissioner will grant an extension of the effective date for reformulation and relabeling for up to two years after the date of publication in the FEDERAL REGISTER.

The Commissioner has set the above effective dates because he concludes that most manufacturers can within 12 months after the date of publication order new labeling and have their products in compliance in the market place. The Commissioner believes that the most reasonable way of dealing with reformulation problems is to extend the date for compliance of a product where the manufacturer is able to demonstrate that he is having significant problems in reformulation and needs additional time to bring his product into compliance.

Therefore, pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040–42 as amended, 1055–56 as amended by 70 Stat. 919 and 72 Stat. 948; 21 U.S.C. 321, 352, 355, 371) and the Administrative Procedure Act (secs. 4, 5, 10, 60 Stat. 238 and 243 as amended; 5 U.S.C. 553, 554, 702, 703, 704) and under authority delegated to him (21 CFR 2.120), and based upon the administrative record in this proceeding, the Commissioner hereby makes the following determinations pursuant to § 330.10(a)(6)–(9) (formerly § 130.301(a)(6)–(9)) of the conditions under which OTC antacid drug products are not generally recognized as safe and effective or are misbranded (Category II), or for which there are insufficient data available to classify such conditions at this time and for which further testing must be undertaken to justify continued marketing (Category III):

COMMISSIONER'S DETERMINATION OF CONDITIONS UNDER WHICH OTC ANTACID DRUG PRODUCTS ARE NOT GENERALLY RECOGNIZED AS SAFE AND EFFECTIVE OR ARE MISBRANDED (CATEGORY II)

The Commissioner determines that the use of antacids under the following conditions is unsupported by scientific data, and in many instances by sound theoretical reasoning. The Commissioner concludes that the ingredients, labeling, and combination drugs involved shall not be permitted in interstate commerce effective as of 6 months after publication of the final monograph in the FEDERAL REGISTER, until scientific testing supports their use and they are approved by the Food and Drug Administration by amendment of the monograph or by a new drug application.

A. *Active ingredients.* No active ingredients that are not included in the monograph or in Category III have been shown by adequate and reliable scientific evidence to be safe and effective for antacid use.

B. *Labeling.* It is not truthful and accurate to make claims or to use indications on the package label that the product may directly affect "nervous or emotional disturbances", "excessive smoking", "food intolerance", "consumption of alcoholic beverages", "acidosis", "nervous tension headaches", "cold symptoms", and "morning sickness of pregnancy", since the relationship of such phenoma to gastric acidity is both unproven and unlikely.

C. *Drugs combining antacid and other active ingredients.* 1. Antacid-analgesic combinations are irrational for antacid use alone and therefore shall not be labeled or marketed for such use. There is a lack of evidence of effectiveness of any analgesic ingredient for any antacid indication.

2. It is not safe and effective concurrent therapy to add an anticholinergic ingredient to an OTC antacid product, because optimal use of antacids and anticholinergic drugs requires independent adjustment of dosages of each drug, because the addition of an anticholinergic drug in a concentration large enough to have detectable pharmacologic effects would result in a compound too toxic for use in self-medication, and because amounts of anticholinergics safe for OTC use have not been shown to affect gastric secretion or upper gastrointestinal symptoms. Since elderly persons number prominently among antacid users, cycloplegia and urinary retention induced by anticholinergic drugs is a definite risk. Thus, a fixed combination of antacid and anticholinergic will result, regardless of how formulated, in a mixture that is either unsafe or ineffective.

For the same reasons, it also is not safe and effective concurrent therapy to combine antacids with sedative-hypnotic ingredients.

3. It is not rational concurrent therapy for a significant portion of the target population for the label to claim that a combination product (e.g., mineral oil and magnesium hydroxide) is to be used both as an antacid and as a laxative, if the laxative claim is based upon use of a non-antacid laxative ingredient. (Active antacid ingredients will be reviewed by the OTC Laxative Panel to determine whether they are effective as laxatives at higher doses than those used for antacid action.)

4. There are no reliable scientific data showing that the addition of an antipeptic agent to an antacid product increases the product's effectiveness as an antacid or is otherwise effective as a means of managing upper gastrointestinal symptoms. No claim for antipeptic activity will be considered truthful and accurate until it is substantiated both by scientifically valid in vitro tests showing that the antipeptic action is substantially greater than that of an agent with only antacid action (such as sodium bicarbonate), and it is proved by studies that the antipeptic activity is clinically meaningful and therefore contributes significantly to the product's effectiveness.

5. The addition of proteolytic agents or bile or bile salts to antacid products is unsafe. Since pepsin is presumably involved in the pathogenesis of peptic ulcer, the addition of pepsin to antacid products may be potentially harmful. Since bile and bile salts can damage gastric mucosa, and since they may be involved in the pathogenesis of gastric ulcer, these substances should not be permitted in antacid products.

6. The addition of an antiemetic to an antacid product is not rational concurrent therapy for a significant portion of the target population.

COMMISSIONER'S DETERMINATION OF OTC ANTACID DRUG PRODUCT CONDITIONS FOR WHICH THE AVAILABLE DATA ARE INSUFFICIENT TO PERMIT FINAL CLASSIFICATION AT THIS TIME (CATEGORY III)

The Commissioner determines that adequate and reliable scientific evidence is not available at this time to permit final classification of the following conditions of use of OTC antacid drug products.

A. *Active ingredients.* These ingredients have either no or negligible antacid action, and there is inadequate evidence of their effectiveness for their non-antacid action in the relief of upper gastrointestinal symptoms or in their adjuvant or corrective properties. Marketing under these conditions may continue for a period of 2 years after the date of publication of this determination if the manufacturer or distributor of the product promptly undertakes adequate testing to prove effectiveness, and if any product that claims to be an antacid (i.e., neutralize stomach acid) meets the in vitro antacid effectiveness standard

contained in the monograph. Products which do not meet both of these requirements shall be subject to the requirements for Category I products. If testing is promptly undertaken but data adequate to prove effectiveness are not submitted to the Food and Drug Administration within the 2-year period, the ingredients listed in this category will no longer be permitted, even in a product that meets the in vitro antacid effectiveness standard, because of a lack of evidence that these ingredients make a meaningful contribution to the claimed effect for the product.

1. *Alginic acid.* Although the ingestion of alginic acid-containing products may produce a layer of material floating on top of the gastric contents, the available evidence is insufficient to demonstrate clinical effectiveness. The studies are fragmentary, uncontrolled, and few in number. No evidence is presented as to reproducibility of results. There is insufficient evidence that alginic acid-containing antacid products, even if they do produce a floating layer on top of the gastric contents, are clinically beneficial. Indeed, such evidence as there is indicates that these products do not increase the pH of gastric contents as a whole. Since regurgitation of gastric contents is particularly apt to occur when patients are lying down rather than in the upright position, alginic acid-containing products may be less beneficial than a standard antacid which is more likely to increase the pH throughout the gastric contents.

Alginic acid is safe in amounts usually taken orally (e.g., 4 grams per day) in antacid products.

2. *Attapulgite (activated).* This ingredient is safe in the amounts usually taken orally in antacid products.

3. *Charcoal, activated.* Charcoal is presently considered safe in amounts usually taken orally in antacid products, but study is specifically needed to determine whether the charcoal used contains benzpyrene or methylcholanthrane type carcinogens. Since charcoal-containing products may decrease absorption of certain oral drugs, the label shall bear the following drug interaction precaution: "Drug Interaction Precautions: Do not take this product if you are presently taking any prescription drug."

4. *Gastric mucin.* This ingredient is safe in the amounts usually taken orally in antacid products.

5. *Kaolin.* Kaolin is safe in amounts usually taken orally in antacid products. Since kaolin affects gastro-intestinal absorption, kaolin interferes with the absorption of lincomycin, and therefore the label shall bear the following drug interaction precaution: "Drug Interaction Precautions: Do not take this product if you are presently taking a prescription antibiotic drug containing lincomycin."

6. *Methylcellulose.* Methylcellulose is safe in amounts usually taken orally e.g., 2 grams per day in antacid products).

7. *Pectin.* Pectin is safe in the amounts usually taken orally in antacid products.

8. *Carboxy methylcellulose.* Carboxy methylcellulose is safe in amounts usually taken (e.g., 3 grams per day) in antacid products.

B. *Labeling.* Marketing under the following labeling conditions may continue for a period of 2 years after the date of publication of this determination subject to the same requirements specified above for the use of Category III ingredients.

1. OTC products containing ingredients listed in Category I or III are often used to treat symptoms that are not known to be related to acidity of gastric contents. These products may or may not qualify as antacids by the in vitro acid neutralizing test. The symptoms include "indigestion", "gas", "upper abdominal pressure", "full feeling", "nausea", "excessive erructations", "upset stomach", and the like. Some of these symptoms are vague, most are poorly understood as to pathophysiological mechanism, and none has been shown by adequate and reliable scientific evidence to be caused by or alleviated by changes in gastric acidity.

2. Claims or indications which link certain signs and symptoms, such as "sour breath", "upper abdominal pressure", "full feeling", "nausea", "stomach distress", "indigestion", "upset stomach", and "excessive eructations" with normal or hypernormal gastric acidity, are unproven since the relationship of such signs and symptoms to gastric acidity is unknown or dubious and there is no adequate and reliable scientific evidence to support these claims. Such claims or indications encourage the user to draw conclusions as to the cause or intermediation of such symptoms, a conclusion that even the medical profession is incapable of drawing at this time.

3. The evidence currently available is inadequate to support the claim that such properties as "floating", "coating", defoaming", "demulcent", and "carminative" contribute to the relief of upper gastrointestinal symptoms. The continued use of such claims, or ones closely allied to them, requires additional studies both to confirm the claimed specific action and to demonstrate clinical significance.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040–42 as amended, 1050–53 as amended, 1055–56 as amended by 70 Stat. 919 and 72 Stat. 948; 21 U.S.C. 321, 352, 355, 371) and the Administrative Procedure Act (secs. 4, 5, 10, 60 Stat. 238 and 243 as amended; 5 U.S.C. 553, 554, 702, 703, 704) and under authority delegated to the Commissioner (21 CFR 2.120) and based upon the administrative record in this proceeding, Title 21 of the Code of Federal Regulations is amended by adding Parts 331 and 332 (formerly §§ 130.305 and 130.306) to Subchapter D to read as follows:

Subpart A—General Provisions

Sec.
331.1 Scope.

Subpart B—Active Ingredients

331.10 Antacid active ingredients.
331.11 Listing of specific active ingredients.
331.15 Combination with nonantacid active ingredients.

Subpart C—Testing Procedures

331.20 Apparatus and reagents.
331.21 Determination of percent contribution of active ingredients.
331.22 Reagent standardization.
331.23 Temperature standardization.
331.24 Tablet disintegration test.
331.25 Preliminary antacid test.
331.26 Acid neutralizing capacity test.
331.29 Test modifications.

Subpart D—Labeling

331.30 Labeling of antacid products.
331.31 Professional labeling.

Subpart A—General Provisions

§ 331.1 Scope.

An over-the-counter antacid product in a form suitable for oral administration is generally recognized as safe and effective and is not misbranded if it meets each of the following conditions and each of the general conditions established in § 330.1 of this chapter.

Subpart B—Active Ingredients

§ 331.10 Antacid active ingredients.

(a) The active antacid ingredients of the product consist of one or more of the ingredients permitted in § 331.11 within any maximum daily dosage limit established, each ingredient is included at a level that contributes at least 25 percent of the total acid neutralizing capacity of the product, and the finished product contains at least 5 mEq. of acid neutralizing capacity and results in a pH of 3.5 or greater at the end of the initial 10-minute period as measured by the method established in § 331.25. The method established in § 331.21 shall be used to determine the percent contribution of each antacid active ingredient.

(b) This section does not apply to an antacid ingredient specifically added as a corrective to prevent a laxative or constipating effect.

§ 331.11 Listing of specific active ingredients.

(a) Aluminum-containing active ingredients:

(1) Aluminum carbonate.

(2) Aluminum hydroxide (or as aluminum hydroxide-hexitol stabilized polymer, aluminum hydroxide-magnesium carbonate codried gel, aluminum hydroxide-magnesium trisilicate codried gel, aluminum-hydroxide sucrose powder hydrated).

(3) Dihydroxyaluminum aminoacetate and dihydroxyaluminum aminoacetic acid.

(4) Aluminum phosphate, maximum daily dosage limit 8 grams.

(5) Dihydroxyaluminum sodium carbonate.

(b) Bicarbonate-containing active ingredients: Bicarbonate ion; maximum

daily dosage limit 200 mEq. for persons up to 60 years old and 100 mEq. for persons 60 years or older.

(c) Bismuth-containing active ingredients:

(1) Bismuth aluminate.
(2) Bismuth carbonate.
(3) Bismuth subcarbonate.
(4) Bismuth subgallate.
(5) Bismuth subnitrate.

(d) Calcium-containing active ingredients: Calcium, as carbonate or phosphate; maximum daily dosage limit 160 mEq. calcium (e.g., 8 grams calcium carbonate).

(e) Citrate-containing active ingredients: Citrate ion, as citric acid or salt; maximum daily dosage limit 8 grams.

(f) Glycine (aminoacetic acid).

(g) Magnesium-containing active ingredients:

(1) Hydrate magnesium aluminate activated sulfate.
(2) Magaldrate.
(3) Magnesium aluminosilicates.
(4) Magnesium carbonate.
(5) Magnesium glycinate.
(6) Magnesium hydroxide.
(7) Magnesium oxide.
(8) Magnesium trisilicate.

(h) Milk solids, dried.

(i) Phosphate-containing active ingredients:

(1) Aluminum phosphate; maximum daily dosage limit 8 grams.
(2) Mono or dibasic calcium salt; maximum daily dosage limt 2 grams.
(3) Tricalcium phosphate; maximum daily dosage limit 24 grams.

(j) Potassium-containing active ingredients:

(1) Potassium bicarbonate (or carbonate when used as a component of an effervescent preparation); maximum daily dosage limit 200 mEq. of bicarbonate ion for persons up to 60 years old and 100 mEq. of bicarbonate ion for persons 60 years or older.
(2) Sodium potassium tartrate.

(k) Sodium-containing active ingredients:

(1) Sodium bicarbonate (or carbonate when used as a component of an effervescent preparation); maximum daily dosage limit 200 mEq. of sodium for persons up to 60 years old and 100 mEq. of sodium for persons 60 years or older, and 200 mEq. of bicarbonate ion for persons up to 60 years old and 100 mEq. of bicarbonate ion for persons 60 years or older. The warning required by § 330.1(g) concerning overdoses is not required on a product containing only sodium bicarbonate powder.
(2) Sodium potassium tartrate.

(l) Silicates:

(1) Magnesium aluminosilicates.
(2) Magnesium trisilicate.

(m) Tartrate-containing active ingredients. Tartaric acid or its salts; maximum daily dosage limit 200 mEq. (15 grams) of tartrate.

§ 331.15 Combination with nonantacid active ingredients.

(a) An antacid may contain any generally recognized as safe and effective nonantacid laxative ingredient to correct for constipation caused by the antacid. No labeling claim of the laxative effect may be used for such a product.

(b) An antacid may contain any generally recognized as safe and effective analgesic ingredient(s), if it is indicated for use solely for the concurrent symptoms involved, e.g., headache and acid indigestion, and is marketed in a form intended for ingestion as a solution.

(c) An antacid may contain any generally recognized as safe and effective antiflatulent ingredient if it is indicated for use solely for the concurrent symptoms of gas associated with heartburn, sour stomach or acid indigestion.

Subpart C—Testing Procedures

§ 331.20 Apparatus and reagents.

(a) pH meter, equipped with glass and saturated calomel electrodes.
(b) Magnetic stirrer.
(c) Magnetic stirring bars (about 40 mm. long and 10 mm. in diameter).
(d) 50 ml. buret.
(e) Buret stand.
(f) 100 ml. beakers.
(g) 250 ml. beakers.
(h) 10 ml., 20 ml. and 30 ml. pipets calibrated to deliver.
(i) Tablet comminuting device.
(j) A number 20 and 100 U.S. standard mesh sieve.
(k) Tablet disintegration apparatus.
(l) 0.1 N, 0.5 N and 1.0 N hydrochloric acid.
(m) 0.5 N sodium hydroxide.
(n) Standard pH 4.0 buffer solution (0.05 M potassium hydrogen phthalate).
(o) 95 percent ethanol.
(p) Distilled Water.

§ 331.21 Determination of percent contribution of active ingredients.

To determine the percent contribution of an antacid active ingredient, place an accurately weighed amount of the antacid active ingredient equal to the amount present in a unit dose of the product into a 250 ml. beaker. If wetting is desired, add not more than 5 ml. of 95 percent ethanol and mix thoroughly to wet the sample (ethanol may affect the acid neutralizing capacity). Add water to a volume of 70 ml. and mix on magnetic stirrer at 300±30 r.p.m. for about one minute. Analyze the sample according to the procedure set forth in § 331.26 and calculate the percent contribution of the antacid active ingredient in the total product as follows:

$$\text{Percent contribution} = \frac{\text{Total mEq. Antacid Active Ingredient} \times 100}{\text{Total mEq. Antacid Product}}$$

§ 331.22 Reagent standardization.

Standardize the sodium hydroxide (NaOH) and Hydrochloric acid (HCl) solutions according to the procedures in the United States Pharmacopeia XVIII (NaOH page 1036 and HCl page 1034) or the Official Methods of Analysis of the Association of Official Analytical Chemists, 11th Ed., 1970, (NaOH page 876 and HCl page 873).[1]

§ 331.23 Temperature standardization.

All tests shall be conducted at 25° C± 3°.

§ 331.24 Tablet disintegration test.

A tablet disintegration test shall be performed on tablets that are not to be chewed following the procedures described in the United States Pharmacopeia XVIII (page 932). If the label states the tablet may be swallowed, it must disintegrate within a 10-minute time limit pursuant to the test procedure using simulated gastric fluid test solution without enzymes, the United States Pharmacopeia XVIII page 1026, rather than water as the immersion fluid.

§ 331.25 Preliminary antacid test.

(a) *pH meter.* Standardize the pH meter at pH 4.0 with the standardizng buffer and check for proper operation at pH 1 with 0.1 N HCl.

(b) *Dosage form testing*—(1) *Liquid sample.* Place an accurately weighed (calculate density) and well mixed amount of the antacid product equivalent to the minimum labeled dosage; e.g., 5 ml., into a 100 ml. beaker. Add sufficient water to obtain a total volume of about 40 ml. and mix on magnetic stirrer at 300±30 r.p.m. for about one minute. Analyze the sample according to the procedure set forth in § 331.25.

(2) *Chewable and non-chewable tablet sample.* Place an accurately weighed amount of a tablet composite equivalent to the minimum labeled dosage into a 100 ml. beaker. (The composite shall be prepared by determining the average weight of not less than 20 tablets and then comminuting the tablets sufficiently to pass through a number 20 U.S. standard mesh sieve and held by a number 100 U.S. standard mesh sieve.) Mix the sieved material to obtain a uniform sample. If wetting is desired, add not more than 5 ml. of 95 percent ethanol and mix to wet the sample thoroughly (ethanol may effect the acid neutralizing capacity). Add water to a volume of 40 ml. and mix on magnetic stirrer at 300±30 r.p.m. for about one minute. (Capsules should be tested in the same manner using the sieved capsule powder as the sample.) Analyze the sample according to the procedure set forth in § 331.25.

(3) *Effervescent sample.* Place an amount equivalent to the minimum labeled dosage into a 100 ml. beaker. Add 10 ml. water and swirl the beaker gently while allowing the reaction to subside. Add another 10 ml. of water and swirl the beaker gently. Wash down the walls of the beaker with 20 ml. of water and

[1] Copies may be obtained from: Association of Official Analytical Chemists, P.O. Box 540, Benjamin Franklin Station, Washington, DC 20044.

mix on magnetic stirrer at 300±30 r.p.m. for about one minute. Analyze the sample according to the procedure set forth in § 331.25.

(4) *Chewing gum samples with antacid in coating.* Place the number of pieces of gum equivalent to the minimum labeled dosage in a 100 ml. beaker. Add 40 ml. of water and mix on magnetic stirrer at 300±30 r.p.m. for about 2 to 3 minutes. Analyze the sample according to the procedure set forth in § 331.25.

(c) *Test procedure.* (1) Add 10.0 ml. 0.5 N HCl to the test solution while stirring on the magnetic stirrer at 300±30 r.p.m.

(2) Stir for exactly 10 minutes after addition of acid.

(3) Read and record pH.

(4) If pH is below 3.5, the product shall not be labeled as an antacid. If the pH is 3.5 or greater, determine the acid neutralizing capacity according to the procedure set forth in § 331.26.

§ 331.26 Acid neutralizing capacity test.

(a) *pH meter.* Standardize the pH meter at pH 4.0 with the standardizing buffer and check for proper operation at pH 1 with 0.1 N HCl.

(b) *Dosage form testing*—(1) *Liquid sample.* Place an accurately weighed (calculate density) and well mixed amount of product equivalent to the minimum labeled dosage (e.g., 5 ml., etc.) into a 250 ml. beaker. Add sufficient water to obtain a total volume of about 70 ml. and mix on the magnetic stirrer at 300±30 r.p.m. for about one minute. Analyze the sample according to the procedure set forth in § 331.26.

(2) *Chewable and non-chewable tablet sample.* Place an accurately weighed amount of a tablet composite equivalent to the minimum labeled dosage into a 250 ml. beaker. (The composite shall be prepared by determining the average weight of not less than 20 tablets and then comminuting the tablets sufficiently to pass through a number 20 U.S. standard mesh sieve and held by a number 100 U.S. standard mesh sieve. Mix the sieved material to obtain a uniform sample.) If wetting is desired, add not more than 5 ml. of 95 percent ethanol and mix to wet the sample thoroughly (ethanol may effect the acid neutralizing capacity). Add water to a volume of 70 ml. and mix on magnetic stirrer at 300±30 r.p.m. for about one minute. (Capsules should be tested in the same manner using the sieved capsule powder as the sample.) Analyze the sample according to the procedure set forth in § 331.26.

(3) *Effervescent sample.* Place an amount equivalent to the minimum labeled dosage into a 250 ml. beaker. Add 10 ml. water and swirl the beaker gently while allowing the reaction to subside. Add another 10 ml. of water and swirl the beaker gently. Wash down the walls of the beaker with 50 ml. of water and mix on magnetic stirrer at 300±30 r.p.m. for about one minute. Analyze the sample according to the procedure set forth in § 331.26.

(4) *Sample and test procedure for chewing gum with antacid in coating.* Assay six pieces of gum individually in the following manner.

(i) Place one piece of gum in a 250 ml. beaker and add 50 ml. of water.

(ii) Pipette in 30.0 ml. of 1.0 N HCl and stir on magnetic stirrer at 300±30 r.p.m.

(iii) Stir for exactly 10 minutes after addition of acid.

(iv) Stop the stirrer and remove the gum using a long needle or similar utensil.

(v) Rinse the long needle or utensil and the gum with 20 ml. of water into the sample beaker.

(vi) Stir for exactly 5 additional minutes.

(vii) Begin titrating immediately and in a period of time not to exceed 5 minutes titrate the exeess 1.0 N HCl with 0.5 N NaOH to stable pH of 3.5.

(viii) Check sample solution 10 to 15 seconds after obtaining pH 3.5 to determine that the pH is stable.

(ix) Average the results of the six individual assays and calculate the total mEq. based on the minimum labeled dosage as follows:

mEq./piece of gum = (30.0 ml.) (normality of HCl) − (ml. of NaOH) (normality of
mEq./piece of gum = (30.0 ml.) (normality
dose = (number of pieces of gum in minimum dosage) × (mEq./piece of gum).

(c) *Acid neutralizing capacity test procedure (except chewing gum).* (1) Pipette 30.0 ml. of 1.0 N HCl into the sample solution while stirring on the magnetic stirrer at 300±30 r.p.m.

(2) Stir for exactly 15 minutes after addition of acid.

(3) Begin titrating immediately and in a period not to exceed an additional 5 minutes titrate the excess 1.0 N HCl with 0.5 N NaOH to stable pH of 3.5.

(4) Check the sample solution 10 to 15 seconds after obtaining pH 3.5 to make sure the pH is stable.

(5) Calculate the number of mEq. of acid neutralized by the sample as follows:

Total mEq. = (30.0 ml.) (normality of HCl) − (ml. of NaOH) (N of NaOH).

Use appropriate factors, i.e., density, average tablet weight, etc., to calculate the total mEq. of acid neutralized per minimum labeled dosage.

§ 331.29 Test modifications.

The formulation and/or mode of administration of certain products may require modification of this in vitro test. Any proposed modification and the data to support it shall be submitted to the Food and Drug Administration for approval prior to use.

Subpart D—Labeling

§ 331.30 Labeling of antacid products.

(a) *Indications.* The labeling of the product represents or suggests the product as an "antacid" to alleviate the following symptoms: "Heartburn," "sour stomach," and/or "acid indigestion."

(b) *Warnings.* The labeling of the product contains the following warnings, under the heading "Warnings", which may be combined but not rearranged to eliminate duplicative words or phrases if the resulting warning is clear and understandable:

(1) "Do not take more than (maximum recommended daily dosage, broken down by age groups if appropriate, expressed in units such as tablets or teaspoonfuls) in a 24-hour period, or use the maximum dosage of this product for more than 2 weeks, except under the advice and supervision of a physician."

(2) For products which cause constipation in 5 percent or more of persons who take the maximum recommended dosage: "May cause constipation."

(3) For products which cause laxation in 5 percent or more of persons who take the maximum recommended dosage: "May have laxative effect."

(4) For products containing more than 50 mEq. of magnesium in the recommended daily dosage: "Do not use this product except under the advice and supervision of a physician if you have kidney disease."

(5) For products containing more than 5 mEq. sodium in the maximum recommended daily dose: "Do not use this product except under the advice and supervision of a physician if you are on a sodium restricted diet."

(6) For products containing more than 25 mEq. potassium in the maximum recommended daily dose: "Do not use this product except under the advice and supervision of a physician if you have kidney disease."

(7) For products containing more than 5 gm per day lactose in a maximum daily dosage: "Do not use this product except under advice and supervision of a physician if you are allergic to milk or milk products."

(c) *Drug interaction precautions.* The labeling of the product contains the following drug interaction precautions, under the heading "Drug Interaction Precautions":

(i) If the product is an aluminum containing antacid: "Do not take this product if you are presently taking a prescription antibiotic drug containing any form of tetracycline."

(d) *Directions for use.* The labeling of the product contains the recommended dosage, under the heading "Directions", per time interval (e.g., every 4 hours) or time period (e.g., 4 times a day) broken down by age groups if appropriate, followed by "or as directed by a physician."

(e) *Statement of sodium containing ingredients.* The labeling of the product contains the sodium content per dosage unit (e.g., tablet, teaspoonful) if it is 0.2 mEq. (5 mg.) or higher.

§ 331.31 Professional labeling.

(a) The labeling of the product provided to health professionals (but not to the general public):

(1) Shall after June 4, 1976 contain the neutralizing capacity of the product as calculated using the procedure set forth in § 331.26 expressed in terms of the dosage recommended per minimum time interval or, if the labeling recommends more than one dosage, in terms of the minimum dosage recommended

per minimum time interval. For compliance purposes, the value determined by the acid neutralizing test at any point in time shall be at least 90 percent of the labeled value. No product shall be marketed with an acid neutralizing capacity below 5 mEq.

(2) May contain an indication for the symptomatic relief of hyperacidity associated with the diagnosis of peptic ulcer, gastritis, peptic esophagitis, gastric hyperacidity, and hiatal hernia.

(b) Professional labeling for an antacid-antiflatulent combination may contain the information allowed for health professionals for antacids and antiflatulents.

PART 332—ANTIFLATULENT PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

Sec.
332.1 Scope.

Subpart B—Active Ingredients

332.10 Antiflatulent active ingredients.
332.15 Combination with non-antiflatulent active ingredients.

Subpart C—[Reserved]

Subpart D—Labeling

332.30 Labeling of antiflatulent products.
332.31 Professional labeling.

Subpart A—General Provisions

§ 332.1 Scope.

An over-the-counter antiflatulent product in a form suitable for oral administration is generally recognized as safe and effective and is not misbranded if it meets each of the following conditions and each of the general conditions established in § 330.1 of this chapter.

Subpart B—Active Ingredients

§ 332.10 Antiflatulent active ingredients.

Simethicone; maximum daily dose 500 mg. There is no dosage limitation at this time for professional labeling.

§ 332.15 Combination with non-antiflatulent active ingredients.

An antiflatulent may contain any generally recognized as safe and effective antacid ingredient(s) if it is indicated for use solely for the concurrent symptoms of gas associated with heartburn, sour stomach or acid indigestion.

Subpart C—[Reserved]

Subpart D—Labeling

§ 332.30 Labeling of antiflatulent products.

(a) *Indications.* The labeling of the product represents or suggests the product as an "antiflatulent" and/or "to alleviate or relieve the symptoms of gas."

(b) *Directions for use.* The labeling of the product contains the recommended dosage per time interval (e.g., every 4 hours) or time period (e.g., 4 times a day) broken down by age groups if appropriate, followed by "except under the advice and supervision of a physician." The words "or as needed" may be used after the recommended dosage per time interval or time period.

§ 332.31 Professional labeling.

(a) The labeling of the product provided to health professionals (but not to the general public) may contain as additional indications postoperative gas pain or for use in endoscopic examination.

(b) Professional labeling for an antiflatulent-antacid combination may contain information allowed for health professionals for antacids and antiflatulents.

Effective date. This order shall become effective on July 5, 1974, except that all labeling for products not receiving an extension of the effective date for reformulation shall become effective on June 4, 1975, and where reformulation is necessary and an extension is granted shall become effective on June 4, 1976. The labeling of a product to health professionals shall after June 4, 1976, contain the neutralizing capacity of the product as calculated using the procedure set forth in § 331.26.

Dated: May 29, 1974.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Part 330]

CLASSIFICATION OF OVER-THE-COUNTER (OTC) DRUGS

Proposal To Designate the Contents and the Time of Closing of the Administrative Record

In the FEDERAL REGISTER of May 11, 1972 (37 FR 9464), the Commissioner of Food and Drugs promulgated procedures governing the review and classification of over-the-counter (OTC) drug products. Questions have recently been raised about the contents of the administrative record on the basis of which the decision is made with respect to the status of an OTC drug product pursuant to these procedures, and the point beyond which new factual information may no longer be submitted for consideration in the administrative process. The Commissioner has concluded that it is appropriate to publish a proposal to add provisions to the regulations to settle these matters.

THE CONTENTS OF THE ADMINISTRATIVE RECORD

Comments filed on the proposed OTC drug review procedures, published in the FEDERAL REGISTER of January 5, 1972 (37 FR 85) had suggested that the final regulation should designate the administrative record on which the administrative decision would be based, for purposes of court appeal. The Commissioner responded in paragraph 82 of the preamble to the final regulation (37 FR 9471) that:

> The record for any court appeal will include all pertinent documentation of the proceeding, including the panel report(s), summary minutes, proposed monograph, tentative final monograph, transcript of oral hearing, final monograph, all comments or objections filed with the Hearing Clerk on the proposed and tentative final monographs, and all data and information received by the panel and made publicly available through the Hearing Clerk. The record for appeal will be compiled by the Office of General Counsel. There is no need to specify these details in the regulations.

A comment on the proposal had also requested that a full transcript of each panel meeting be made public, which presumably would then have been a part of the administrative record. The Commissioner responded to this comment in paragraph 37 of the preamble to the final regulation, stating that a verbatim transcript of all panel meetings would not be necessary in view of the extensive procedural safeguards set out in the regulation and the fact that the OTC drug panels only report recommendations to the Commissioner, who must then make the final decisions after full public procedure.

Thus, the preamble to the final OTC drug review procedural regulations explicitly designated the contents of the administrative record and excluded any transcript that may be made of any panel meeting.

The Commissioner published in the FEDERAL REGISTER of January 8, 1974 (39 FR 1359) a notice of a public hearing to be held on the tentative final order for OTC antacid drug products, pursuant to the provisions of § 330.10(a)(8) (formerly § 130.301(a)(8)) of the regulations. The notice reiterated the content of the administrative record as designated in the preamble to the final order establishing the procedural regulations for the OTC drug review.

In response to this notice, an objection was received on the designation of the administrative record. The objection contended that the complete transcript of the meetings of the Panel should be included as part of the administrative record. The Food and Drug Administration replied that such transcripts are exempt from public disclosure under the Freedom of Information Act, 5 U.S.C. 552(b)(5), and that in any event they are not considered by the Commissioner in the formulation of his decisions and orders and thus do not properly constitute part of the administrative record. The Food and Drug Administration stated that, in order to avoid any possible confusion on this matter, the procedural regulations would be amended explicitly to state this fact.

The Commissioner is obligated to base his decision with respect to a monograph on the entire administrative record. In the case of the final antacid monograph, which is published elsewhere in this issue of the FEDERAL REGISTER, the Commissioner has not at any time read or referred to or relied upon the words recorded in the transcripts of the Antacid Panel meetings. Rather, he has relied solely upon the minutes of the Panel meetings, the data and information submitted to and considered by the Panel, the Panel report, the comments submitted on that report, the tentative final order, the objections submitted on the tentative final order, the transcript of and material submitted at the public hearing, and comments permitted to be filed subsequent to the public hearing. This constitutes the administrative record specified in the notice of May 11, 1972, and is the sole basis on which the proposal, the tentative final order, and the final order were made by the Commissioner. The Commissioner has concluded that the same procedure will be followed for his consideration of future OTC drug monographs.

The irrelevance of the transcripts of the panel deliberations can perhaps best be described by an analogy. The transcripts reflect deliberations and debates among a group of individuals prior to arriving at a final recommendation. The group, in this instance, is deliberating upon recommendations with respect to regulatory policy that will ultimately have the force and effect of law. Their deliberations are therefore directly analogous to the deliberations of a panel of judges of a United States Court of Appeals. It is obvious that the judges who hear a case deliberate among themselves with respect to the issues involved. Moreover, it would not be unusual that there will be several drafts of an opinion, and that the final decision might be quite different from the initial discussions or even tentative drafts. The final opinion written by the court, however, is the only document appealable to or reviewed by the United States Supreme Court. The deliberations of the Court of Appeals, and their various drafts reflecting intermediate considerations and positions, are not a part of the record and are not reviewed by the Supreme Court. The final opinion must stand or fall on its own merits. The same is true of the final reports of the OTC drug review panels. They stand or fall on their own merits, and are either supported or unsupported by the medical and scientific evidence submitted to and considered by the panel.

The logic of this position is further compelled by the fact that not all panel deliberations are recorded or transcribed. Although some transcription or recording occurs with most of the OTC drug review panels, it is necessarily incomplete. Panel members frequently confer by telephone with each other, discuss matters over lunch and dinner, and talk about them during breaks and in the corridors. Moreover, the major reflective consideration of the issues involved would be likely to occur before and after meetings, when the panel members individually review the data and information and form their conclusions with respect to it. Thus, any transcript of panel deliberations would reflect only a part, and perhaps a small part, of the consideration given to the matter, of the reasoning which lies behind the recommendations ultimately made, and thus of the entire deliberative process. It would therefore be highly improper to consider the transcripts of panel meetings in determining the validity of the final OTC antacid drug monograph.

Moreover, the purely deliberative portions of a panel's discussion during which it formulates its conclusions and recommendations are lawfully closed to the public and any transcripts relating to this portion of the meetings are therefore properly retained as confidential under 5 U.S.C. 552(b)(5) rather than as part of the public administrative record.

The legal justification for closing the deliberative portion of a panel's discussions, i.e., the discussion during which the panel determines its conclusions and recommendation—and retaining the transcripts of those closed portions as confidential may be found in section 10 of the Federal Advisory Committee Act and exemption (5) of the Freedom of Information Act. Section 10(a)(1) of the Federal Advisory Committee Act provides that each advisory committee meeting shall be open to the public. Section 10(d) then provides that paragraph (a)(1) shall not apply to any advisory committee meeting which the head of the agency determines is concerned with matters listed in 5 U.S.C. 552(b), and requires that any such determination shall be in writing and shall contain the reasons therefor.

The authority to close the Food and Drug Administration advisory committee meetings has been delegated to the Commissioner, subject to the concurrence of the office of General Counsel. 21 CFR 2.120(a)(18). In exercising his authority to close portions of advisory committee meetings pursuant to this delegation, the Commissioner has acted on the basis of the guidelines established by the Office of Management and Budget and the Department of Justice as set out in the FEDERAL REGISTER of January 23, 1973 (38 FR 2306). The Commissioner's formal written determination to close a portion of a meeting is published together with the notice of the meeting in the FEDERAL REGISTER.

The basis on which the purely deliberative portions of panel discussions have been closed pursuant to section 10(d) of the Federal Advisory Committee Act is that the discussions are concerned with matters covered by 5 U.S.C. 552(b)(5), i.e., internal communications. As the Attorney General's Memorandum of June 1967 on this portion of the Freedom of Information Act states:

> * * * internal communications which would not routinely be available to a party in litigation with the agency, such as internal drafts, memoranda between officials or agencies, opinions and interpretations prepared by agency staff personnel or consultants for the use of the agency, and records of the deliberations of the agency or staff groups, remain exempt so that free exchange of ideas will not be inhibited. As the President stated upon signing the new law, "officials within the government must be able to communicate with one another fully and frankly without publicity.

All of the panel members are, of course, consultants to the Food and Drug Administration and, as such, government employees during their period of actual work on the panel. The discussion within a panel therefore stands on no different footing than a discussion within an internal Food and Drug Administration staff meeting.

At the same time, the Commissioner recognizes that, consistent with the Federal Advisory Committee Act, advisory committee proceedings should remain open to public view and include participation to the maximum extent feasible. It is for this reason that all interested persons are provided an opportunity to make written submissions to each panel and to present oral views to the panel. The Commissioner has concluded, however, that the deliberations of the panels during which their conclusions and recommendations are determined could not reasonably be made in open session, and thus that it is essential to avoid undue interference with the regulatory process that they be closed to the public.

The primary reason for closing such deliberative portions of advisory committee meetings is, of course, because of the regulatory nature of the action being considered. With respect to the OTC drug review, the issues involve the possibility of specific law enforcement action against an individual product, e.g., requiring relabeling of the drug or new testing by the manufacturer, or removing the product from the market completely. The panel discussions include a continuous admixture of deliberations on interim regulatory decisions, and thus much of the panel discussion is closed to protect the integrity of the regulatory process.

Accordingly, the Commissioner proposes to amend § 330.10 to designate the contents of the administrative record upon which his decision on a monograph shall be based, and to exclude the transcripts of any panel meetings from that designation. The decision will be required to be based solely upon the administrative record so designated and not upon any data, information, or materials not included as part of such record. Court appeal will then be based solely upon that record and the information it contains.

CLOSING OF THE ADMINISTRATIVE RECORD

The notice published in the FEDERAL REGISTER of January 8, 1974 (39 FR 1359) announcing the public hearing on the tentative final order for OTC antacid drug products also stated that, since this was a hearing on the administrative record, only data and information submitted at an earlier stage in the proceeding would be considered. The notice stated that any new data or information could be discussed only if such material were first submitted to the Commissioner with a petition to reopen the administrative record to include such new material, justifying why it was not submitted earlier, and the Commissioner granted the petition.

One objection was received to this notice, contending that this requirement was not included in § 330.10 (formerly § 130.301) of the regulations. In reply, the Food and Drug Administration stated that, although it believed that the procedural regulations made it clear that new evidence could not for the first time be submitted at the public hearing on the tentative final order, such evidence would be accepted as an exception on that occasion and that the procedural regulations would then be amended to prevent recurrence of this problem in the future.

It is standard procedural practice before all administrative bodies and courts that the record in any proceeding is closed at some specified point in time to prevent continuous submission of new data and information. Thereafter in the proceeding, arguments and contentions may be made solely on the basis of the data and information already contained in the record, and new data or information can be filed only with the permission of the presiding officer upon sound justification why the material was not submitted earlier.

The Commissioner concludes that, in the OTC drug review, submission of new data and information should be permitted only through the 60-day period permitted under § 330.10(a)(6) (formerly § 130.301(a)(6)) for comment on the proposed monograph. Thereafter, all rebuttal comments, objections, and statements at the oral hearing must be based solely upon the administrative record developed through that time. Permission to submit additional data or information may be granted, in the sole discretion of the Commissioner, on the basis of a petition to reopen the administrative record to include such material. Any such petition shall demonstrate good cause why such material could not have been obtained and submitted in response to the initial call for data and information or as part of the comments on the proposed monograph. If such a petition is not granted, such material is properly submitted with a subsequent petition to amend the monograph.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040–42 as amended, 1050–53 as amended, 1055–56 as amended by 70 Stat. 919 and 72 Stat. 948; (21 U.S.C. 321, 352, 355, 371)) and the Administrative Procedure Act (secs. 4, 10, 60 Stat. 238 and 243 as amended; (5 U.S.C. 553, 702, 703, 704)) and under authority delegated to him (21 CFR 2.120), the Commissioner proposes to amend 21 CFR Part 330 by redesignating § 330.10(a)(10) through (13) as (a)(11) through (14) and by adding a new § 330.10(a)(10) to read as follows:

§ 330.10 Procedures for classifying OTC drugs as generally recognized as safe and effective and not misbranded, and for establishing monographs.

* * * * *

(a) * * *

(10) *Administrative record.* (i) All data and information to be considered in any proceeding pursuant to this section shall be submitted in response to the request for data and views pursuant to paragraph (a)(2) of this section or accepted by the panel during its deliberations pursuant to paragraph (a)(3) of this section or submitted to the Hearing Clerk as part of the comments during the 60-day period permitted pursuant to paragraph (a)(6) of this section. Thereafter, no new data or information may be submitted for inclusion in the administrative record of such proceeding except as provided in paragraph (a)(10)(ii) of this section.

(ii) New data or information not previously submitted for inclusion in the administrative record may be submitted for such inclusion only with a petition to the Commissioner requesting that the administrative record be reopened to include such material. The Commissioner may grant or deny such petition in his discretion. Any such petition shall demonstrate good cause why such material could not be obtained and submitted within the time specified in paragraph (a)(10)(i) of this section. If such a petition is denied, such material is properly submitted with a petition to amend the monograph pursuant to paragraph (a)(12) of this section.

(iii) The Commissioner shall make all decisions and issue all orders pursuant to this section solely on the basis of the

administrative record, and shall not consider data or information not included as part of the administrative record.

(iv) The administrative record shall consist solely of the following material: All notices and orders published in the FEDERAL REGISTER, all data and views submitted in response to the request published pursuant to paragraph (a)(2) of this section or accepted by the panel during its deliberations pursuant to paragraph (a)(3) of this section, all minutes of panel meetings, the panel report(s), all comments and rebuttal comments submitted on the proposed monograph pursuant to paragraph (a)(6) of this section, all objections submitted on the tentative final monograph pursuant to paragraph (a)(7) of this section, the complete record of any oral public hearing conducted pursuant to paragraph (a)(8) of this section, all other comments requested at any time by the Commissioner, all data and information for which the Commissioner has reopened the administrative record, and all other material which the Commissioner includes in the administrative record as part of the basis for his decision.

* * * * *

Interested persons may, on or before July 5, 1974 file with the Hearing Clerk, Food and Drug Administration, Room 6–86, 5600 Fishers Lane, Rockville, MD 20852, written comments (preferably in quintuplicate) regarding this proposal. Comments may be accompanied by a memorandum or brief in support thereof. Received comments may be seen in the above office during working hours, Monday through Friday.

Dated: May 29, 1974.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

[FR Doc.74–12663 Filed 6–3–74;8:45 am]

[21 CFR Part 330]

OTC DRUGS

Proposed General Conditions

In the FEDERAL REGISTER of November 12, 1973 (38 FR 31258) the Commissioner of Food and Drugs promulgated general conditions for OTC drugs that are generally recognized as safe and effective and are not misbranded. Section 330.1(g) (formerly § 130.302(g)) included a general warning: "Keep this and all drugs out of the reach of children. In case of accidental overdose, contact a physician immediately." Section 330.1(i) (formerly § 130.302(i)) included the following drug interaction warning: "Warning: Do not take this product concurrently with a prescription drug except on the advice of a physician." The effective date of that order was December 12, 1973.

A number of written comments were received in response to that order. The Commisisoner also entertained comments on § 330.1 (g) and (i) and related issues at the public hearing that was held on January 21, 1974, pursuant to the notice published in the FEDERAL REGISTER of January 8, 1974 (39 FR 1359). In view of these written and oral comments, the Commissioner has concluded to reopen this matter and to propose a new version of the general warning in § 330.1(g) and to revoke the drug interaction warning in § 330.1(i).

There was comment that the words "consult your poison control center" should be added to the general warning under § 330.1(g) (formerly § 130.302(g)).

The Commissioner concurs that it would be in the best interest of the consumer to have knowledge that there is more than one source of professional assistance available. For that reason the Commissioner proposes to amend the statement to read: "Keep this and all drugs out of the reach of children. In case of accidental overdose, seek professional assistance or contact your poison control center immediately".

Many of the comments relating to the drug interaction warning under § 330.1 (i) (formerly § 130.302(i)) stated that the pharmacist is a qualified health professional who is available, able, and educated to give advice to consumers concerning OTC products and drug interactions.

The Commissioner agrees that the pharmacist is a qualified health professional and does have knowledge about drug interactions and OTC medications.

There was also comment that, because of his knowledge and availability, the pharmacist should be included as a source of information in the drug interaction warning statement in § 330.1(i).

The Commissioner believes that the consumer should have available every source of reliable, helpful drug information. The proposal and final order stated that the patient's physician should be consulted on possible drug interactions because only he would be certain to know the identity of any prescription drugs being taken concurrently by the patient. It has been brought to the Commissioner's attention that other health professionals, such as physicians' assistants, nurses, nurse practitioners, dentists, and pharmacists, also may have this information and may be more readily available for consultation.

After a great deal of discussion and review, the Commissioner has concluded that the proper way to handle possible drug interactions is to require that the labeling include a separate section headed "Drug Interaction Precautions," stating the specific or general interaction problem involved with that particular OTC drug. Thus, in the final monograph on OTC antacid drugs published elsewhere in this issue of the FEDERAL REGISTER, a drug interaction precaution has been included for all aluminum-containing OTC antacid drug products stating that they should not be used concurrently with tetracycline. The same format will be used for other specific drug interactions found to exist in other monographs. Where known drug interactions exist but are not limited to a specific drug, the precaution statement shall be phrased in terms of general drug categories, such as has been required for charcoal which has been determined to be in Category III under the final order on OTC antacid drug products.

The Commissioner believes that this approach is more consistent with the concept of OTC drug labeling and with providing the most complete and useful information to consumers in concise terms. It directly advises the consumer that the drugs described are not to be used concurrently because of a possible drug interaction.

The purpose of OTC medication is to permit consumers to engage in self-medication without medical or other professional supervision, or in any event with the least amount of supervision feasible. Directing that consumers consult health professionals of any type would seem appropriate only if it is concluded that this is the only possible method of assuring the safe and effective use of the drug. Accordingly, although the Commissioner recognizes the availability of useful drug information through all health professionals, he concludes that it is unnecessary and inappropriate that they be designated on the label in any manner with respect to this particular matter in view of the availability of fully informative labeling which obviates such reference.

The Commissioner recognizes that all health professionals will continue to be a source of sound information on drugs, and encourages recent trends toward training of such persons in pharmacology and toxicology. The Commissioner also recognizes that, on occasion, a physician will wish to direct a patient to continue to use an OTC drug concurrently with a prescription drug contrary to a drug interaction precaution, where they are administered in a way that precludes interaction or other circumstances necessitate such action. In addition, consumers will be fully informed and protected by these labeling precautions.

The Commissioner has considered whether a standard format for a drug interaction precaution should be adopted. In view of the fact that no standard format for label warnings or other label statements has been prescribed in the section on general conditions, the Commissioner has concluded that there is no need to establish such a standard format in this instance. The format utilized in the final order for antacid drug products published elsewhere in this issue of the FEDERAL REGISTER will be utilized in future monographs except where good reason exists to vary from it. Accordingly, the Commissioner is proposing to revoke the warning as it presently exists in § 330.1(i) (formerly § 130.302(i)) of the regulations.

There were some comments by pharmacy organizations that a so-called "third class of drugs," under the control of pharmacists should be created by the Food and Drug Administration. The term "third class of drugs" has a slightly different meaning to different organizations. Some organizations would have the product dispensed only in a phar-

macy, others would have the product dispensed only by a pharmacist, and still others would require that the pharmacist keep a drug dispensing record similar to prescription drug records. The particular mechanics of a third class of drugs are not a significant issue as related to the Commissioner's appraisal of this proposal. Some comments specified that all OTC drugs with a drug interaction warning should be in this third class of drugs, and contended that the two issues are inseparable.

The Commissioner has spent a great deal of time reviewing the comments and discussing this issue with various groups, both in and out of the profession of pharmacy. The Federal Food, Drug, and Cosmetic Act requires that OTC drugs be safe and effective for lay use. Although the act permits imposition of whatever limitations or restrictions are necessary to assure the safe use of any drug, including restrictions on the channels of distribution, no controlled studies or other adequate research data have been supplied to support the position that any class of OTC drugs must be dispensed only by pharmacists in order to assure their safe use. It would be inappropriate to restrict the sale of OTC drugs to pharmacies based on anything less than proof that a significant safety issue was involved.

There were a number of comments stating that creating a third class of drugs would create an economic monopoly and an anticompetitive situation. The Department of Justice opposed any such restriction on antitrust grounds.

The Commissioner believes that these concerns are valid. Restricting the sale of some or all OTC drugs only to pharmacies would decrease the number of outlets where the consumer could purchase OTC products, limit competition, and raise some OTC drug prices, with no attendant public benefit. There is at this time no public health concern that would justify the creation of a third class of drugs to be dispensed only by a pharmacist or in a pharmacy. The "third class of drug" issue at this time is solely an economic issue. The Commissioner therefore categorically rejects the establishment of a third class of drugs at this time.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040–1042, as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948; (21 U.S.C. 321, 352, 355, 371)), the Administrative Procedure Act (secs. 4, 5, 10, 60 Stat. 238 and 243 as amended; (5 U.S.C. 553, 554, 702, 703, 704)) and under authority delegated to the Commissioner (21 CFR 2.120), it is proposed that 21 CFR Part 330 be amended by revoking § 330.1(i) and by revising § 330.1(g) to read as follows:

§ 330.1 General conditions for general recognition as safe, effective and not misbranded.

* * * * *

(g) The labeling contains the general warning: "Keep this and all drugs out of the reach of children. In case of accidental overdose, seek professional assistance or contact a poison control center immediately." The Food and Drug Administration will grant an exemption from this general warning where appropriate upon petition.

* * * * *

(i) [Revoked]

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Interested persons are invited to submit their comments in writing (preferably in quintuplicate) regarding this proposal on or before August 5, 1974. Comments should be filed with the Hearing Clerk, Food and Drug Administration, Rm. 6–86, 5600 Fishers Lane, Rockville, MD 20852, and may be accompanied by a memorandum or brief in support thereof. Received comments may be seen in the above office during working hours, Monday through Friday.

Dated: May 29, 1974.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

[FR Doc.74–12665 Filed 6–3–74;8:45 am]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[Docket No. FDC–D–135, etc.; NDA 1–875, etc.]

OVER-THE-COUNTER ANTACID DRUG PRODUCTS

Opportunity for Hearing on Proposal To Withdraw Approval of New Drug Applications

Elsewhere in this issue of the FEDERAL REGISTER the Commissioner of Food and Drugs is promulgating a final order determining the conditions under which over-the-counter (OTC) antacid drug products are generally recognized as safe and effective and are not misbranded, and which therefore may be marketed without an approved new drug application. After the applicable effective date of that order, any over-the-counter antacid product must either comply with such conditions or, if it does not, be shown to be safe and effective and not misbranded for its claimed uses pursuant to an approved new drug application.

The Director of the Bureau of Drugs has reviewed all new drug applications for OTC antacid products, whether pre-1962 or post-1962, and concludes that none of those described below, specifically or by reference, either complies with all of the conditions for safety, effectiveness, and labeling stated in the final order on OTC antacid drug products, or contains the evidence required by the act to support any conditions of use other than those permitted by that order.

On the basis of all of the data and information now available to him, the Director of the Bureau of Drugs is unaware of any adequate and well-controlled clinical investigation conducted by experts qualified by scientific training and experience meeting the requirements of section 505 of the Act, § 314.111(a)(5) (formerly § 130.12(a)(5)), and, where applicable, 21 CFR 3.86 for fixed combination drugs, demonstrating the effectiveness of the drugs for any condition of use other than those permitted by the final order on OTC antacid products published elsewhere in this issue of the FEDERAL REGISTER; or of adequate tests by all methods reasonably applicable to show that any of the conditions required or excluded for safety reasons by the final order on OTC antacid drug products should not be so required or excluded. To the extent that the labeling of products subject to or covered by NDA's differs from the applicable labeling requirements set forth in the final order on OTC antacid products, the Director concludes, on the basis of the information before him and on a fair evaluation of all material facts, that such labeling is false and misleading. Accordingly, the Director concludes that it is necessary to withdraw approval of the new drug applications and to determine the new drug status of the affected products.

It is unnecessary for any manufacturer or distributor of an antacid drug product which complies with the requirements of 21 CFR Part 331 or the interim requirements for Category III drug products specified in the Commissioner's final order on OTC antacid drugs, published elsewhere in this issue of the FEDERAL REGISTER, to submit a supplemental or abbreviated or full new drug application covering such a product. In accordance with § 330.10, any such product may lawfully be marketed without an approved new drug application. Accordingly, reformulation and/or relabeling to meet such requirements is sufficient for the continued lawful marketing of any OTC antacid drug product subject to this notice.

1. The following new drug applications were subject to the NAS–NRC Drug Efficacy Study, for which the Food and Drug Administration's conclusions were deferred pending results of the OTC drug review in this class:

NDA	Drug	Firm
1–875	Chooz Chewing Gum.	Pharmaco, Inc., Kenilworth, N.J. 07033.
1–952	Kamat tablets	Cole Pharmacal Co., Inc., St. Louis, Mo. 63178.
2–436	Amphojel tablets	Wyeth Laboratories; division of American Home Products Corp., Philadelphia, Pa. 19101.
2–545	Gelusil liquid	Warner-Chilcott Laboratories, division of Warner-Lambert Co., Morris Plains, N.J. 07950.
3–807	Magsal suspension	Endo Laboratories, Inc., Garden City, Long Island, N.Y. 11530.
4–380	Gelusil tablets	Warner-Chilcott Laboratories, division of Warner-Lambert Co., Morris Plains, N.J. 07950.
5–668	Alglyn tablets, Alglyn magma, Belglun tablets.	Brayten Pharmaceutical Co., Chattanooga, Tenn. 37409.
6–547	Alzinox tablets	Smith, Miller, & Patch, New Brunswick, N.J. 08902.
6–738	Carmethose suspension, Carmethose magnesium oxdie tablets, Carmethose-Trasentine.	Ciba Pharmaceutical Co., division of Ciba-Geigy Corp., Summit, N.J. 07901.
7–706	Resinate capsules, Resinate tablets.	Merrell-National Laboratories, division of Richardson-Merrell, Inc., Cincinnati, Ohio 45215.
7–911	Kolantyl tablets	Merrell-National Laboratories, division of Richardson-Merrell, Inc., Cincinnati, Ohio 45215.
8–431	Dimacid B tablets.	Otis Chapp and Son, Inc., Cambridge, Mass. 02139.
8–467	Kolantyl Gel	Merrell-National Laboratories, division of Richardson-Merrell, Inc., Cincinnati, Ohio 45215.
9–100	Rolaids Antacid Mint tablets.	American Chicle Co., division of Warner-Lambert Co., Morris Plains, N.J. 07950.
12–165	Rolaids Antacid Mint with HMAS.	American Chicle Co., division of Warner-Lambert Co., Morris Plains, N.J. 07950.
12–298	"A" Plus tablets	Vick Chemical Co., division of Richardson-Merrell, Inc., New York, N.Y. 10017.

2. Notices for new drug applications for OTC antacid products for which approval has previously been withdrawn on the ground of failure to file reports required pursuant to section 505(j) of the act appeared in the FEDERAL REGISTER as follows:

a. Docket FDA–D–135 published in the FEDERAL REGISTER of July 24, 1970 (35 FR 11929).

b. Docket FDC–D–259 published in the FEDERAL REGISTER of April 6, 1971 (36 FR 6529).

c. Docket FDC–D–269 (Docket number originally published incorrectly as FDC–D–259; correction published in the FEDERAL REGISTER of November 24, 1971 (36 FR 22324) to read FDC–D–269) published in the FEDERAL REGISTER of August 6, 1971 (36 FR 14493) and republished in the FEDERAL REGISTER of September 23, 1971 (36 FR 18885).

d. Docket FDC–D–445 published in the FEDERAL REGISTER of March 18, 1972 (37 FR 5711).

e. Docket FDC–D–393 published in the FEDERAL REGISTER of March 28, 1972 (37 FR 6342).

f. Docket FDC–D–492 published in the FEDERAL REGISTER of August 8, 1972 (37 FR 15948).

Those notices stated that, at the time of their publication, conclusions concerning safety and effectiveness of the particular products had not yet been reached, and thus those notices did not constitute a determination of the new drug status of the drug products subject to the NDAs or of any identical, similar or related drug products. Notice is hereby given to all manufacturers and distributors of OTC antacid drug products that the legal status of all such OTC antacid drug products has now been determined by the final order on this class of drugs published elsewhere in this issue of the FEDERAL REGISTER, including all drugs identical, related, or similar to drugs for which the new drug applications were withdrawn previously in the above FEDERAL REGISTER notices.

3. The following new drug applications were approved after 1962 or otherwise were not considered by the NAS–NRC in the Drug Efficacy Study:

NDA	Drug	Firm
1–650	Citralka liquid	Parke, Davis & Co., Detroit, Mich. 48232.
3–304	Bismakaolin suspension.	Vale Chemical Co., Inc., Allentown, Pa. 18102.
9–329	Duplexin tablets	Whitehall Laboratories division of American Home Products Corp., New York, N.Y. 10017.
15–183	Equilet Antacid tablets.	Mission Pharmacal Co., San Antonio, Tex. 78296.

Therefore, notice is given to the holder(s) of all of the new drug application(s) specified and referenced above and to all other interested persons that the Director of the Bureau of Drugs pro-

poses to issue an order under section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)), withdrawing approval of the new drug application(s) and all amendments and supplements thereto and determining the new drug status of the affected products on the grounds that, on the basis of new information before him with respect to the drug product(s), evaluated together with the evidence available to him at the time of approval of the application(s), (1) there is a lack of substantial evidence that the drug product(s) will have the effect it purports or is represented to have for any condition of use prescribed, recommended, or suggested in the labeling, other than those permitted by the final order on OTC antacid drug products; and (2) such drug is not shown to be safe for use except under the conditions of use required for safety reasons, and is not shown to be safe for use under the conditions of use excluded for safety reasons, by the final order on OTC antacid drug products; and (3) the labeling of the drug product(s), to the extent it differs from the applicable labeling requirements of the final order on OTC antacid drug products, based on a fair evaluation of all material facts, is false or misleading.

In addition to the holder(s) of the new drug application(s) specifically named above or included by reference to notices previously withdrawing approval, this notice of opportunity for hearing applies to all persons who manufacture or distribute a drug product which is identical, related, or similar to a drug product named or referenced above, as defined in 21 CFR 310.6. It is the responsibility of every drug manufacturer or distributor to review this notice of opportunity for hearing to determine whether it covers any drug product he manufactures or distributes. Any person may request an opinion of the applicability of this notice to a specific drug product he manufactures or distributes that may be identical, related, or similar to a drug product named or included by reference in this notice by writing to the Food and Drug Administration, Bureau of Drugs, Office of Compliance (HFD-300), 5600 Fishers Lane, Rockville, MD 20852.

In addition to the ground(s) for the proposed withdrawal of approval stated above, this notice of opportunity for hearing encompasses all issues relating to the legal status of the drug products subject to it (including identical, related, or similar drug products as defined in § 310.6), e.g., any contention that any such product is not a new drug because it is generally recognized as safe and effective within the meaning of section 201(p) of the act or because it is exempt from part or all of the new drug provisions of the act pursuant to the exemption for products marketed prior to June 25, 1938, contained in section 201(p) of the act, or pursuant to section 107(c) of the Drug Amendments of 1962; or for any other reason.

In accordance with the provisions of section 505 of the act (21 U.S.C. 355) and the regulations promulgated thereunder (21 CFR 310, 314), the applicant(s) and all other persons subject to this notice pursuant to 21 CFR 310.6 are hereby given an opportunity for a hearing to show why approval of the new drug application(s) should not be withdrawn and an opportunity to raise, for administrative determination, all issues relating to the legal status of a drug product named above and of all identical, related, or similar drug products.

If an applicant or any other person subject to this notice pursuant to 21 CFR 310.6 elects to avail himself of the opportunity for a hearing, he shall file (1) on or before July 5, 1974, a written notice of appearance and request for hearing, and (2) on or before August 5, 1974, the data, information, and analyses on which he relies to justify a hearing, as specified in 21 CFR 314.200. Any other interested person may also submit comments on this notice. The procedures and requirements governing this notice of opportunity for hearing, a notice of appearance and request for hearing, a submission of data, information, and analyses to justify a hearing, other comments, and a grant or denial of hearing, are contained in 21 CFR 130.14 and discussed in detail as published in the FEDERAL REGISTER of March 13, 1974 (39 FR 9750), recodified as 21 CFR 314.200, published in the FEDERAL REGISTER of March 29, 1974 (39 FR 11680).

The failure of an applicant or any other person subject to this notice pursuant to 21 CFR 310.6 to file timely written appearance and request for hearing as required by 21 CFR 314.200 constitutes an election by such person not to avail himself of the opportunity for a hearing concerning the action proposed with respect to such drug product and a waiver of any contentions concerning the legal status of any such drug product. Any such drug product may not lawfully be marketed except in compliance with 21 CFR Part 331 or the interim requirements for Category III drug products specified in the Commissioner's final order on OTC antacid drugs, published elsewhere in this issue of the FEDERAL REGISTER. The Food and Drug Administration will initiate appropriate regulatory action to remove such noncomplying drug products from the market promptly after the applicable effective date established in that order.

A request for a hearing may not rest upon mere allegations or denials, but must set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. If it conclusively appears from the face of the data, information, and factual analyses in the request for the hearing that there is no genuine and substantial issue of fact which precludes the withdrawal of approval of the application, or when a request for hearing is not made in the required format or with the required analyses, the Commissioner will enter summary judgment against the person(s) who requests the hearing, making findings and conclusions, denying a hearing.

All submissions pursuant to this notice shall be filed in quintuplicate with the Hearing Clerk, Food and Drug Administration (HFC-20), Room 6-86, 5600 Fishers Lane, Rockville, MD 20852.

All submissions pursuant to this notice except for data and information prohibited from public disclosure pursuant to 21 U.S.C. 331(j) or 18 U.S.C. 1905, may be seen in the office of the Hearing Clerk during regular business hours, Monday through Friday.

This notice is issued pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (sec. 505, 52 Stat. 1052-53, as amended (21 U.S.C. 355)), and under authority delegated to the Director of the Bureau of Drugs (21 CFR 2.121).

Dated: May 29, 1974.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

[FR Doc.74-12664 Filed 6-3-74;8:45 am]